



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>C07D 403/04, 401/14, 403/14, A61K 31/40, C07D 403/06, 405/14, 409/14, 471/04</b>		A1	(11) International Publication Number: <b>WO 95/32196</b>
			(43) International Publication Date: 30 November 1995 (30.11.95)
(21) International Application Number: PCT/GB95/01129		Andrew [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). STREET, Leslie, Joseph [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).	
(22) International Filing Date: 18 May 1995 (18.05.95)			
(30) Priority Data:		(74) Agent: THOMPSON, John; Merck & Co., Inc., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).	
9410080.7	19 May 1994 (19.05.94)	GB	(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).
9411954.2	15 June 1994 (15.06.94)	GB	
9415805.2	4 August 1994 (04.08.94)	GB	
9425448.9	16 December 1994 (16.12.94)	GB	
(71) Applicant (for all designated States except US): MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB).		Published With international search report.	
(72) Inventors; and (75) Inventors/Applicants (for US only): CASTRO PINEIRO, Jose, Luis [ES/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). CHAMBERS, Mark, Stuart [GB/GB]; Terlings Park, Harlow, Essex CM20 2QR (GB). HOBBS, Sarah, Christine [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). MATASSA, Victor, Giulio [GB/IT]; Istituto Ricerche Di Biologia Molecolare, Via Pontina Km. 30,600, I-00040 Pomezia (IT). REEVE, Austin, John [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). SHOWELL, Graham,			
(54) Title: PIPERAZINE, PIPERIDINE AND TETRAHYDROPYRIDINE DERIVATIVES OF INDOL-3-YLALKYL AS 5-HT <sub>1D</sub> -ALPHA AGONISTS			
(57) Abstract			
<p>Compounds of formula (I), or a salt or prodrug thereof, wherein Z represents an optionally substituted five-membered heteroaromatic ring selected from furan, thiophene, pyrrole, oxazole, thiazole, isoxazole, isothiazole, imidazole, pyrazole, oxadiazole, thiadiazole, triazole and tetrazole; E represents a chemical bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms; Q represents a straight or branched alkylene chain containing from 1 to 6 carbon atoms, optionally substituted in any position by a hydroxy group; T represents nitrogen or CH; U represents nitrogen or C-R<sup>2</sup>; V represents oxygen, sulphur or N-R<sup>3</sup>; -F-G- represents -CH<sub>2</sub>-N-, -CH<sub>2</sub>-CH- or -CH=C-; R<sup>1</sup> represents C<sub>3-6</sub> alkenyl, C<sub>3-6</sub> alkynyl, aryl(C<sub>1-6</sub>)alkyl or heteroaryl(C<sub>1-6</sub>)alkyl, any of which groups may be optionally substituted; and R<sup>2</sup> and R<sup>3</sup> independently represent hydrogen or C<sub>1-6</sub> alkyl are selective agonists of 5-HT<sub>1</sub>-like receptors, being potent agonists of the human 5-HT<sub>1Dα</sub> receptor subtype, whilst processing at least a 10-fold selective affinity for the 5-HT<sub>1Dα</sub> receptor subtype, relative to the 5-HT<sub>1Dβ</sub> subtype; they are therefore useful in the treatment and/or prevention of clinical conditions, in particular migraine and associated disorders, for which a subtype-selective agonist of 5-HT<sub>1D</sub> receptors is indicated, whilst eliciting fewer side-effects, notably adverse cardiovascular events, than those associated with non-subtype-selective 5-HT<sub>1D</sub> receptor agonists.</p>			

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

PIPERAZINE, PIPERIDINE AND TETRAHYDROPYRIDINE DERIVATIVES OF INDOL-3-YLALKYL  
AS 5-HT<sub>1D</sub>-ALPHA AGONISTS

The present invention relates to a class of substituted  
5 piperazine, piperidine and tetrahydropyridine derivatives which act on  
5-hydroxytryptamine (5-HT) receptors, being selective agonists of so-called  
"5-HT<sub>1</sub>-like" receptors. They are therefore useful in the treatment of  
clinical conditions for which a selective agonist of these receptors is  
indicated.

10 It has been known for some time that 5-HT<sub>1</sub>-like receptor  
agonists which exhibit selective vasoconstrictor activity are of use in the  
treatment of migraine (see, for example, A. Doenicke *et al.*, *The Lancet*,  
1988, Vol. 1, 1309-11).

The human 5-HT<sub>1</sub>-like or 5-HT<sub>1D</sub> receptor has recently been  
15 shown by molecular cloning techniques to exist in two distinct subtypes.  
These subtypes have been termed 5-HT<sub>1D $\alpha$</sub>  (or 5-HT<sub>1D-1</sub>) and 5-HT<sub>1D $\beta$</sub>  (or  
5-HT<sub>1D-2</sub>), and their amino acid sequences are disclosed and claimed in  
WO-A-91/17174.

The 5-HT<sub>1D $\alpha$</sub>  receptor subtype in humans is believed to reside  
20 on sensory terminals in the dura mater. Stimulation of the 5-HT<sub>1D $\alpha$</sub>   
subtype inhibits the release of inflammatory neuropeptides which are  
thought to contribute to the headache pain of migraine. The human  
5-HT<sub>1D $\beta$</sub>  receptor subtype, meanwhile, is located predominantly on the  
blood vessels and in the brain, and hence may play a part in mediating  
25 constriction of cerebral and coronary arteries, as well as CNS effects.

Administration of the prototypical 5-HT<sub>1D</sub> agonist  
sumatriptan (GR43175) to humans is known to give rise at therapeutic  
doses to certain adverse cardiovascular events (see, for example, F. Willett  
*et al.*, *Br. Med. J.*, 1992, 304, 1415; J.P. Ottervanger *et al.*, *The Lancet*,  
30 1993, 341, 861-2; and D.N. Bateman, *The Lancet*, 1993, 341, 221-4). Since  
sumatriptan barely discriminates between the human 5-HT<sub>1D $\alpha$</sub>  and

5-HT<sub>1D $\beta$</sub>  receptor subtypes (cf. WO-A-91/17174, Table 1), and since it is the blood vessels with which the 5-HT<sub>1D $\beta$</sub>  subtype is most closely associated, it is believed that the cardiovascular side-effects observed with sumatriptan can be attributed to stimulation of the 5-HT<sub>1D $\beta$</sub>  receptor subtype. It is accordingly considered (cf. G.W. Rebeck *et al.*, *Proc. Natl. Acad. Sci. USA*, 1994, 91, 3666-9) that compounds which can interact selectively with the 5-HT<sub>1D $\alpha$</sub>  receptor subtype, whilst having a less pronounced action at the 5-HT<sub>1D $\beta$</sub>  subtype, might be free from, or at any rate less prone to, the undesirable cardiovascular and other side-effects associated with non-subtype-selective 5-HT<sub>1D</sub> receptor agonists, whilst at the same time maintaining a beneficial level of anti-migraine activity.

The compounds of the present invention, being selective 5-HT<sub>1</sub>-like receptor agonists, are accordingly of benefit in the treatment of migraine and associated conditions, e.g. cluster headache, chronic paroxysmal hemicrania, headache associated with vascular disorders, tension headache and paediatric migraine. In particular, the compounds according to this invention are potent agonists of the human 5-HT<sub>1D $\alpha$</sub>  receptor subtype. Moreover, the compounds in accordance with this invention have been found to possess at least a 10-fold selective affinity for the 5-HT<sub>1D $\alpha$</sub>  receptor subtype relative to the 5-HT<sub>1D $\beta$</sub>  subtype, and they can therefore be expected to manifest fewer side-effects than those associated with non-subtype-selective 5-HT<sub>1D</sub> receptor agonists.

Several distinct classes of substituted five-membered heteroaromatic compounds are described in published European patent applications 0438230, 0497512 and 0494774, and published International patent applications 93/18029, 94/02477 and 94/03446. The compounds described therein are stated to be agonists of 5-HT<sub>1</sub>-like receptors, and accordingly to be of particular use in the treatment of migraine and associated conditions. None of these publications, however, discloses nor even suggests the piperazine, piperidine and tetrahydropyridine derivatives provided by the present invention.

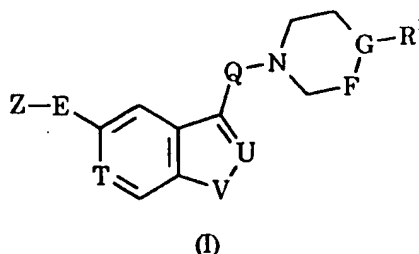
In EP-A-0548813 is described a series of alkoxy pyridin-4-yl and alkoxy pyrimidin-4-yl derivatives of indol-3-ylalkylpiperazines which are alleged to provide treatment of vascular or vascular-related headaches, including migraine. There is, however, no disclosure nor any suggestion in EP-A-0548813 of replacing the alkoxy pyridine or  
5 alkoxy pyrimidine substituent with an optionally substituted alkenyl, alkynyl, aryl-alkyl or heteroaryl-alkyl substituent; nor is there any suggestion therein that the range of substituents specified at the 5-position of the indole moiety might be successfully replaced by an  
10 optionally substituted five-membered heteroaromatic ring.

Moreover, nowhere in the prior art available to date is there any disclosure of a subtype-selective 5-HT<sub>1D</sub> receptor agonist having a 5-HT<sub>1D $\alpha$</sub>  receptor binding affinity (IC<sub>50</sub>) below 50 nM and at least a 10-fold selective affinity for the 5-HT<sub>1D $\alpha$</sub>  receptor subtype relative to the 5-HT<sub>1D $\beta$</sub>   
15 subtype.

In one aspect, therefore, the present invention provides a subtype-selective 5-HT<sub>1D</sub> receptor agonist having a 5-HT<sub>1D $\alpha$</sub>  receptor binding affinity (IC<sub>50</sub>) below 50 nM and at least a 10-fold selective affinity for the 5-HT<sub>1D $\alpha$</sub>  receptor subtype relative to the 5-HT<sub>1D $\beta$</sub>  subtype. In a  
20 preferred embodiment of this aspect, the present invention provides a subtype-selective 5-HT<sub>1D</sub> receptor agonist having a 5-HT<sub>1D $\alpha$</sub>  receptor binding affinity (IC<sub>50</sub>) below 10 nM and at least a 50-fold selective affinity for the 5-HT<sub>1D $\alpha$</sub>  subtype relative to the 5-HT<sub>1D $\beta$</sub>  subtype.

In another aspect, the present invention provides a  
25 compound of formula I, or a salt or prodrug thereof:

- 4 -



wherein

Z represents an optionally substituted five-membered heteroaromatic ring selected from furan, thiophene, pyrrole, oxazole, thiazole, isoxazole, isothiazole, imidazole, pyrazole, oxadiazole, thiadiazole, triazole and tetrazole;

E represents a chemical bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;

Q represents a straight or branched alkylene chain containing from 1 to 6 carbon atoms, optionally substituted in any position by a hydroxy group;

T represents nitrogen or CH;

U represents nitrogen or C-R<sup>2</sup>;

V represents oxygen, sulphur or N-R<sup>3</sup>;

-F-G- represents -CH<sub>2</sub>-N-, -CH<sub>2</sub>-CH- or -CH=C-;

R<sup>1</sup> represents C<sub>3-6</sub> alkenyl, C<sub>3-6</sub> alkynyl, aryl(C<sub>1-6</sub>)alkyl or heteroaryl(C<sub>1-6</sub>)alkyl, any of which groups may be optionally substituted; and

R<sup>2</sup> and R<sup>3</sup> independently represent hydrogen or C<sub>1-6</sub> alkyl.

The present invention also provides compounds of formula I above wherein T represents CH; R<sup>1</sup> represents aryl(C<sub>1-6</sub>)alkyl or heteroaryl(C<sub>1-6</sub>)alkyl, either of which groups may be optionally substituted; and Z, E, Q, U, V, F and G are as defined above.

The present invention further provides compounds of formula I above wherein Q represents a straight or branched alkylene chain containing from 1 to 6 carbon atoms; T represents CH; R<sup>1</sup> represents

aryl(C<sub>1-6</sub>)alkyl or heteroaryl(C<sub>1-6</sub>)alkyl, either of which groups may be optionally substituted; and Z, E, U, V, F and G are as defined above.

The present invention still further provides compounds of formula I above wherein Q represents a straight or branched alkylene chain containing from 1 to 6 carbon atoms; T represents CH; -F-G- represents -CH<sub>2</sub>-N-; R<sup>1</sup> represents aryl(C<sub>1-6</sub>)alkyl or heteroaryl(C<sub>1-6</sub>)alkyl, either of which groups may be optionally substituted; and Z, E, U and V are as defined above.

The present invention yet further provides compounds of formula I above wherein Q represents a straight or branched alkylene chain containing from 1 to 6 carbon atoms; T represents nitrogen; U represents C-R<sup>2</sup>; V represents N-R<sup>3</sup>; -F-G- represents -CH<sub>2</sub>-N-; R<sup>1</sup> represents aryl(C<sub>1-6</sub>)alkyl or heteroaryl(C<sub>1-6</sub>)alkyl, either of which groups may be optionally substituted; and Z, E, R<sup>2</sup> and R<sup>3</sup> are as defined above.

The five-membered heteroaromatic ring Z in the compounds of formula I above may be optionally substituted by one or, where possible, two substituents. As will be appreciated, where Z represents an oxadiazole, thiadiazole or tetrazole ring, only one substituent will be possible; otherwise, one or two optional substituents may be accommodated around the five-membered heteroaromatic ring Z. Examples of suitable substituents on the five-membered heteroaromatic ring Z include C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, aryl, aryl(C<sub>1-6</sub>)alkyl, C<sub>3-7</sub> heterocycloalkyl, heteroaryl, heteroaryl(C<sub>1-6</sub>)alkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylthio, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub>)alkylamino, halogen, cyano and trifluoromethyl.

The group R<sup>1</sup> may be optionally substituted by one or more substituents. Where R<sup>1</sup> represents aryl(C<sub>1-6</sub>)alkyl or heteroaryl(C<sub>1-6</sub>)alkyl, any optional substitution will suitably be on the aryl or heteroaryl moiety thereof, although substitution on the alkyl moiety thereof is an alternative possibility. Examples of optional substituents on the group R<sup>1</sup> include halogen, cyano, trifluoromethyl, triazolyl, tetrazolyl, C<sub>1-6</sub>

- alkyl-tetrazolyl, hydroxy, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylthio, C<sub>2-6</sub> alkoxycarbonyl, C<sub>2-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkylsulphonyl, arylsulphonyl, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylaminomethyl, C<sub>2-6</sub> alkylcarbonylamino, arylcarbonylamino, C<sub>2-6</sub> alkoxycarbonylamino,
- 5 N-(C<sub>1-6</sub>)alkyl-N-(C<sub>2-6</sub>)alkoxycarbonylamino, C<sub>1-6</sub> alkylsulphonylamino, arylsulphonylamino, C<sub>1-6</sub> alkylsulphonylaminomethyl, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonylamino, di(C<sub>1-6</sub>)alkylaminocarbonylamino, mono- or diarylaminocarbonylamino, pyrrolidinylcarbonylamino, piperidinylcarbonylamino, aminocarbonyl, C<sub>1-6</sub>
- 10 alkylaminocarbonyl, di(C<sub>1-6</sub>)alkylaminocarbonyl, aminosulphonyl, C<sub>1-6</sub> alkylaminosulphonyl, di(C<sub>1-6</sub>)alkylaminosulphonyl, aminosulphonylmethyl, C<sub>1-6</sub> alkylaminosulphonylmethyl and di(C<sub>1-6</sub>)alkylaminosulphonylmethyl.

- As used herein, the expression "C<sub>1-6</sub> alkyl" includes methyl
- 15 and ethyl groups, and straight-chained or branched propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and t-butyl. Derived expressions such as "C<sub>1-6</sub> alkoxy", "C<sub>1-6</sub> alkylthio" and "C<sub>1-6</sub> alkylamino" are to be construed accordingly.

- The expression "C<sub>2-6</sub> alkenyl" as used herein refers to
- 20 straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl, allyl, dimethylallyl and butenyl groups.

- The expression "C<sub>2-6</sub> alkynyl" as used herein refers to
- straight-chained and branched alkynyl groups containing from 2 to 6
- 25 carbon atoms. Typical examples include ethynyl and propargyl groups.

Typical C<sub>3-7</sub> cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Typical aryl groups include phenyl and naphthyl.

- The expression "aryl(C<sub>1-6</sub>)alkyl" as used herein includes
- 30 benzyl, phenylethyl, phenylpropyl and naphthylmethyl.



Suitable heterocycloalkyl groups include azetidiny, pyrrolidyl, piperidyl, piperazinyl and morpholinyl groups.

Suitable heteroaryl groups include pyridyl, quinolyl, isoquinolyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl groups.

The expression "heteroaryl(C<sub>1-6</sub>)alkyl" as used herein includes furylmethyl, furylethyl, thienylmethyl, thienylethyl, oxazolylmethyl, oxazolylethyl, thiazolylmethyl, thiazolylethyl, imidazolylmethyl, imidazolylethyl, oxadiazolylmethyl, oxadiazolylethyl, thiadiazolylmethyl, thiadiazolylethyl, triazolylmethyl, triazolylethyl, tetrazolylmethyl, tetrazolylethyl, pyridylmethyl, pyridylethyl, pyrimidinylmethyl, pyrazinylmethyl, quinolylmethyl and isoquinolylmethyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluorine.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible *in vivo* into the required compound of formula I. Conventional  
5 procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in *Design of Prodrugs*, ed. H. Bundgaard, Elsevier, 1985.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers.  
10 Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

The optionally substituted five-membered heteroaromatic  
15 ring Z in formula I is suitably a 1,3-oxazole, 1,3-thiazole, imidazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole or tetrazole ring. Preferably, the ring is a 1,3-oxazole, 1,3-thiazole, 1,2,4-oxadiazole, 1,2,4-thiadiazole or 1,2,4-triazole ring, in particular a 1,2,4-triazol-1-yl or 1,2,4-triazol-4-yl moiety.

20 Suitably, the five-membered heteroaromatic ring Z is unsubstituted. Examples of optional substituents which may typically be attached to the moiety Z include methyl, ethyl, benzyl and amino.

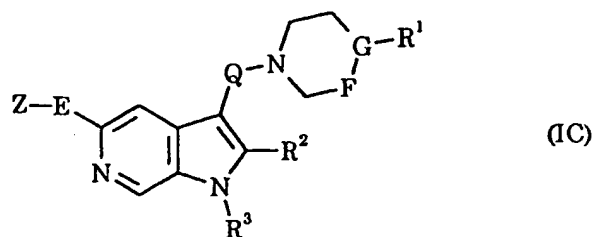
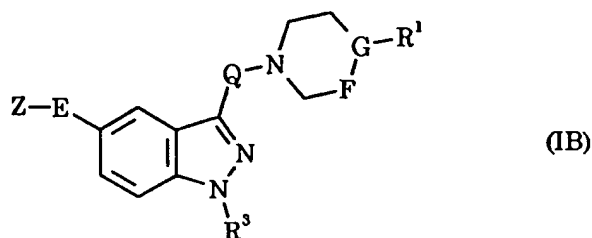
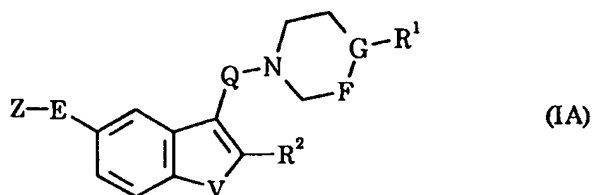
Where E and Q, which may be the same or different, represent straight or branched alkylene chains, these may be, for  
25 example, methylene, ethylene, 1-methylethylene, propylene, 2-methylpropylene or butylene. In addition, the alkylene chain Q may be substituted in any position by a hydroxy group giving rise, for example, to a 2-hydroxypropylene or 2-hydroxymethyl-propylene chain Q. Moreover, E may represent a chemical bond such that the moiety Z is attached  
30 directly to the central fused bicyclic heteroaromatic ring system containing the variables T, U and V.

- 9 -

Suitably, E represents a chemical bond or a methylene linkage.

Representative alkylene chains for Q include propylene, butylene, 2-hydroxypropylene and 2-hydroxymethyl-propylene.

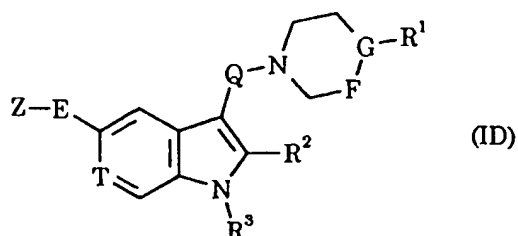
5 The compound of formula I in accordance with the present invention is suitably an indole, benzofuran or benzthiophene derivative of formula IA, an indazole derivative of formula IB, or a pyrrolo[2,3-c]-pyridine derivative of formula IC:



10

wherein Z, E, Q, V, F, G, R¹, R² and R³ are as defined above. Preferably, the compounds according to the invention are indole or pyrrolo[2,3-c]-pyridine derivatives of formula ID:

15

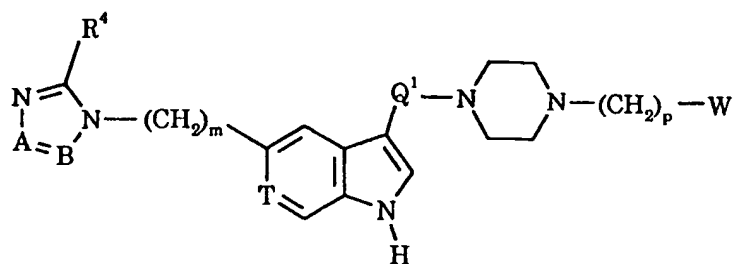


wherein Z, E, Q, T, F, G, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined above, in particular wherein R<sup>2</sup> and R<sup>3</sup> are both hydrogen.

- 5                   Suitable values for the substituent R<sup>1</sup> include allyl, dimethylallyl, butenyl, propargyl, benzyl, phenylethyl, furylmethyl, thienylmethyl, imidazolymethyl and pyridylmethyl, any of which groups may be optionally substituted by one or more substituents selected typically from halogen, cyano, triazolyl, tetrazolyl, C<sub>1-6</sub> alkyl-tetrazolyl,
- 10 C<sub>1-6</sub> alkoxy, amino, di(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylaminomethyl, C<sub>2-6</sub> alkylcarbonylamino, C<sub>2-6</sub> alkoxycarbonylamino, N-(C<sub>1-6</sub>)alkyl-N-(C<sub>2-6</sub>)alkoxycarbonylamino, C<sub>1-6</sub> alkylsulphonylamino, aminocarbonylamino, aminocarbonyl, C<sub>1-6</sub> alkylaminocarbonyl, di(C<sub>1-6</sub>)alkylaminocarbonyl, aminosulphonyl and C<sub>1-6</sub>
- 15 alkylaminosulphonylmethyl.
- Particular values of R<sup>1</sup> include allyl, dimethylallyl, butenyl, propargyl, benzyl, fluorobenzyl, cyanobenzyl, tetrazolyl-benzyl, methyltetrazolyl-benzyl, methoxybenzyl, aminobenzyl, dimethylaminomethyl-benzyl, acetylamino-benzyl, aminocarbonyl-benzyl,
- 20 methylaminocarbonyl-benzyl, dimethylaminocarbonyl-benzyl, aminosulphonyl-benzyl, phenylethyl, cyano-phenylethyl, triazolyl-phenylethyl, amino-phenylethyl, dimethylamino-phenylethyl, acetylamino-phenylethyl, methoxycarbonylamino-phenylethyl, (N-methyl-N-methoxycarbonyl)amino-phenylethyl, aminocarbonylamino-
- 25 phenylethyl, furylmethyl, thienylmethyl, imidazolymethyl, pyridylmethyl and amino-pyridylmethyl.

Suitably,  $R^2$  and  $R^3$  independently represent hydrogen or methyl, especially hydrogen.

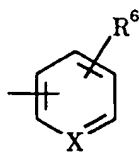
A particular sub-class of compounds according to the invention is represented by the compounds of formula IIA, and salts and  
 5 prodrugs thereof:



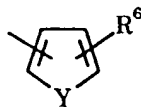
(IIA)

wherein

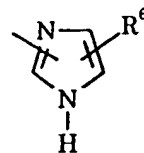
- 10                     $m$  is zero, 1, 2 or 3;  
                        $p$  is 1, 2 or 3;  
                        $Q^1$  represents a straight or branched alkylene chain  
                       containing from 2 to 5 carbon atoms, optionally substituted in any position  
                       by a hydroxy group;
- 15                     $T$  represents nitrogen or  $CH$ ;  
                        $A$  represents nitrogen or  $CH$ ;  
                        $B$  represents nitrogen or  $C-R^5$ ;  
                        $R^4$  and  $R^5$  independently represent hydrogen,  $C_{1-6}$  alkyl,  $C_{2-6}$   
                       alkenyl,  $C_{3-7}$  cycloalkyl, aryl, aryl( $C_{1-6}$ )alkyl,  $C_{3-7}$  heterocycloalkyl,  
 20                    heteroaryl, heteroaryl( $C_{1-6}$ )alkyl,  $C_{1-6}$  alkoxy,  $C_{1-6}$  alkylthio, amino,  $C_{1-6}$   
                       alkylamino, di( $C_{1-6}$ )alkylamino, halogen, cyano or trifluoromethyl; and  
                        $W$  represents a group of formula (a), (b) or (c):



(a)



(b)



(c)

in which

X represents CH or nitrogen;

5 Y represents oxygen, sulphur or NH; and

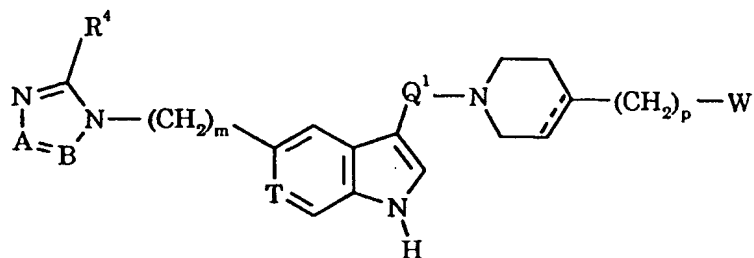
R<sup>6</sup> represents hydrogen, halogen, cyano, trifluoromethyl, triazolyl, tetrazolyl, C<sub>1-6</sub> alkyl-tetrazolyl, C<sub>1-6</sub> alkoxy, C<sub>2-6</sub> alkylcarbonyl, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylaminomethyl, C<sub>2-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulphonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonyl, aminosulphonyl or C<sub>1-6</sub> alkylaminosulphonylmethyl.

10 Suitably, Q<sup>1</sup> represents a straight or branched 3 or 4 carbon alkylene chain, optionally substituted in any position by a hydroxy group. Particular alkylene chains for Q<sup>1</sup> include propylene, butylene, 2-hydroxypropylene and 2-(hydroxymethyl)-propylene.

15 Particular values of R<sup>4</sup> and R<sup>5</sup> include hydrogen, methyl, ethyl, benzyl and amino, especially hydrogen.

Particular values of R<sup>6</sup> include hydrogen, fluoro, cyano, triazolyl, tetrazolyl, methyl-tetrazolyl, methoxy, amino, dimethylaminomethyl, acetylamino, aminocarbonylamino, 20 methylaminocarbonyl and aminosulphonyl.

Another sub-class of compounds according to the invention is represented by the compounds of formula IIB, and salts and prodrugs thereof.



(IIB)

wherein the broken line represents an optional chemical bond; and

m, p, Q<sup>1</sup>, T, A, B, R<sup>4</sup> and W are as defined with reference to  
 5 formula IIA above.

In the compounds of formula IIA and IIB as defined above, Q<sup>1</sup> may represent a group of formula -(CH<sub>2</sub>)<sub>n</sub>- wherein n is 2, 3, 4 or 5, preferably 3 or 4.

The present invention also provides compounds of formula  
 10 IIA and IIB as defined above wherein T represents CH; and R<sup>6</sup> is other than C<sub>1-6</sub> alkyl-tetrazolyl, di(C<sub>1-6</sub>)alkylaminomethyl and C<sub>1-6</sub> alkylaminocarbonyl.

The present invention further provides compounds of formula IIA and IIB as defined above wherein Q<sup>1</sup> represents -(CH<sub>2</sub>)<sub>n</sub>-; T represents  
 15 CH; and R<sup>6</sup> is other than tetrazolyl, C<sub>1-6</sub> alkyl-tetrazolyl, di(C<sub>1-6</sub>)alkylaminomethyl, C<sub>1-6</sub> alkylaminocarbonyl and aminosulphonyl.

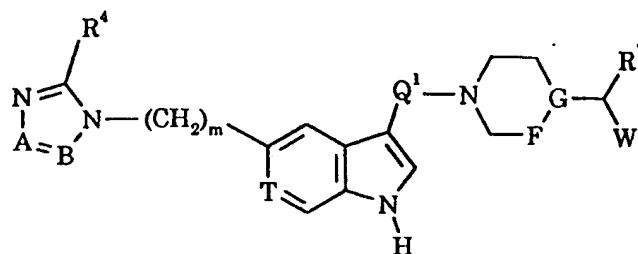
The present invention additionally provides compounds of formula IIA as defined above wherein Q<sup>1</sup> represents -(CH<sub>2</sub>)<sub>n</sub>-; T represents  
 20 CH; and R<sup>6</sup> is other than triazolyl, tetrazolyl, C<sub>1-6</sub> alkyl-tetrazolyl, di(C<sub>1-6</sub>)alkylaminomethyl, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonyl and aminosulphonyl.

The present invention provides in addition compounds of formula IIA as defined above wherein Q<sup>1</sup> represents -(CH<sub>2</sub>)<sub>n</sub>-; T represents nitrogen; and R<sup>6</sup> is other than triazolyl, tetrazolyl, C<sub>1-6</sub> alkyl-tetrazolyl,

- 14 -

di(C<sub>1-6</sub>)alkylaminomethyl, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonyl and aminosulphonyl.

A further sub-class of compounds according to the invention is represented by the compounds of formula IIC, and salts and prodrugs thereof:



(IIC)

wherein

T, F and G are as defined with reference to formula I above;  
m, Q<sup>1</sup>, R<sup>4</sup>, A, B and W are as defined with reference to formula IIA above; and

R<sup>7</sup> represents hydrogen, aminomethyl, C<sub>1-6</sub> alkylaminomethyl, di(C<sub>1-6</sub>)alkylaminomethyl, C<sub>2-6</sub> alkoxy carbonylaminomethyl, [N-(C<sub>1-6</sub>)alkyl-N-(C<sub>2-6</sub>)alkoxy carbonyl]aminomethyl, aminocarbonyl, C<sub>1-6</sub> alkylaminocarbonyl or di(C<sub>1-6</sub>)alkylaminocarbonyl.

Particular values of R<sup>7</sup> include hydrogen, dimethylaminomethyl, methoxycarbonylaminomethyl, (N-methyl-N-methoxycarbonyl)aminomethyl, aminocarbonyl, methylaminocarbonyl and dimethylaminocarbonyl, especially hydrogen.

Specific compounds within the scope of the present invention include:

1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[4-(acetyl amino)phenyl]methylpiperazine;



- 1-[4-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)butyl]-4-[4-(acetylamino)phenyl]methylpiperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-(2-methoxyphenyl)methylpiperazine;
- 5 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-benzylpiperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-(pyridin-3-yl)methylpiperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-(pyridin-2-yl)methylpiperazine;
- 10 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-(pyridin-4-yl)methylpiperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-(4-aminophenyl)methylpiperazine;
- 1-[4-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)butyl]-4-benzylpiperazine;
- 15 1-[4-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)butyl]-4-(pyridin-2-yl)methylpiperazine;
- 1-[4-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)butyl]-4-(pyridin-3-yl)methylpiperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-(4-aminophenyl)ethyl]piperazine;
- 20 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-(4-(acetylamino)phenyl)ethyl]piperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-(imidazol-2-yl)methylpiperazine;
- 25 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[3-(acetylamino)phenyl]methylpiperazine;
- 4-benzyl-1-[3-(5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propyl]piperazine;
- 4-benzyl-1-[3-(5-(1,2,4-triazol-4-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propyl]piperazine;
- 30

- 4-(4-acetylaminophenyl)methyl-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperidine;
- 4-benzyl-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-1,2,5,6-tetrahydropyridine;
- 5 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-(2-aminopyridin-5-yl)methylpiperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-(4-(aminocarbonylamino)phenyl)ethyl]piperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-(4-
- 10 cyanophenyl)methylpiperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-(4-cyanophenyl)ethyl]piperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-(4-(1,2,4-triazol-4-yl)phenyl)ethyl]piperazine;
- 15 1-[3-(5-(1,2,4-triazol-1-yl)-1H-indol-3-yl)propyl]-4-[2-(4-(acetylamino)phenyl)ethyl]piperazine;
- 1-[3-(5-(1,2,4-triazol-1-yl)-1H-indol-3-yl)propyl]-4-benzylpiperazine;
- 1-[3-(5-(1,2,4-triazol-1-yl)methyl)-1H-indol-3-yl)propyl]-4-benzylpiperazine;
- 1-[3-(5-(1,2,4-triazol-1-yl)methyl)-1H-indol-3-yl)propyl]-4-[2-(4-
- 20 (acetylamino)phenyl)ethyl]piperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-(3-(acetylamino)phenyl)ethyl]piperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[4-(aminosulphonyl)phenyl)methyl]piperazine;
- 25 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-(furan-3-yl)methylpiperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-(furan-2-yl)methylpiperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-(thien-2-
- 30 yl)methylpiperazine;

- 1-benzyl-4-[(R,S)-2-hydroxy-3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;
- 1-[2-(4-(acetylamino)phenyl)ethyl]-4-[(R,S)-2-hydroxy-3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;
- 5 1-benzyl-4-[(R,S)-2-hydroxymethyl-3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-(1H-tetrazol-5-yl)phenyl]methylpiperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-(2-phenylethyl)piperazine;
- 10 4-benzyl-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;
- 4-[2-(2-methyltetrazol-5-yl)phenyl]methyl-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;
- 4-[2-(1-methyltetrazol-5-yl)phenyl]methyl-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;
- 15 4-[2-(N-methylcarboxamido)phenyl]methyl-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;
- 4-[2-(N,N-dimethylaminomethyl)phenyl]methyl-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;
- 20 4-(but-3-enyl)-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;
- 4-(3-methylbut-2-enyl)-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;
- 4-(prop-2-enyl)-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;
- 4-(prop-2-ynyl)-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;
- 25 4-[(R,S)-1-(phenyl)carboxamidomethyl]-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;
- (+)-4-[1-(phenyl)carboxamidomethyl]-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;
- (-)-4-[1-(phenyl)carboxamidomethyl]-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;
- 30

- 4-[1-(phenyl)-N-methylcarboxamidomethyl]-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;
- 4-[1-(phenyl)-N,N-dimethylcarboxamidomethyl]-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;
- 5 4-(2-methoxycarbonylamino-1-phenylethyl)-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;
- 4-(2-dimethylamino-1-phenylethyl)-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;
- 4-[2-(4-(acetylamino)phenyl)ethyl]-1-[3-(5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propyl]piperazine;
- 10 4-[2-(4-(acetylamino)phenyl)ethyl]-1-[3-(5-(1,2,4-triazol-4-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propyl]piperazine;
- 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-(4-fluorophenyl)methylpiperazine;
- 15 4-[2-(N-methyl-N-methoxycarbonyl)amino-1-phenylethyl]-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;
- and salts and prodrugs thereof.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a

20 pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral,

parenteral, intranasal, sublingual or rectal administration, or for

25 administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical

30 diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a

pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

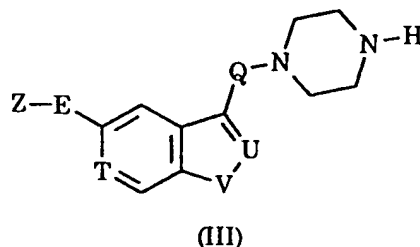
The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of migraine, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day,

- 20 -

and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

The compounds according to the invention wherein -F-G- represents -CH<sub>2</sub>-N- may be prepared by a process which comprises attachment of the R<sup>1</sup> moiety to a compound of formula III:



wherein Z, E, Q, T, U and V are as defined above; by conventional means including N-alkylation.

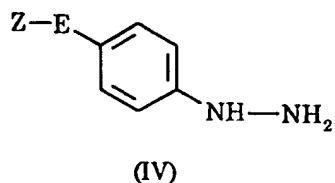
Attachment of the R<sup>1</sup> moiety to the compounds of formula III may conveniently be effected by standard alkylation techniques. One example thereof comprises treatment with an alkenyl halide such as 4-bromobut-1-ene, 4-bromo-2-methylbut-2-ene or allyl bromide, an alkynyl halide such as propargyl bromide, or an aryl(C<sub>1-6</sub>)alkyl or heteroaryl(C<sub>1-6</sub>)alkyl halide such as benzyl iodide, typically under basic conditions, e.g. sodium hydride or potassium carbonate in N,N-dimethylformamide, or triethylamine in acetonitrile. Another example comprises treatment of the compound of formula III with an aryl(C<sub>1-6</sub>)alkyl or heteroaryl(C<sub>1-6</sub>)alkyl mesylate such as 2-(4-cyanophenyl)ethyl methanesulphonate, typically in the presence of sodium carbonate and sodium iodide, in a suitable solvent such as 1,2-dimethoxyethane.

Alternatively, the R<sup>1</sup> moiety may conveniently be attached by reductive alkylation, which may be accomplished in a single step, or as a two-step procedure. The single-step approach suitably comprises treating the required compound of formula III as defined above with the appropriate aldehyde, e.g. benzaldehyde, furfuraldehyde or thiophene

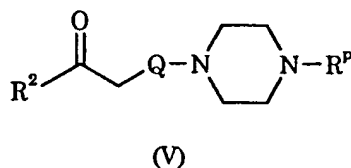
- 21 -

carboxaldehyde, in the presence of a reducing agent such as sodium cyanoborohydride. In a typical two-step procedure, for the preparation of a compound of formula I wherein  $R^1$  corresponds to a group of formula  $-CH_2R^{11}$ , a carboxylic acid derivative of formula  $R^{11}-CO_2H$  is condensed  
 5 with the required compound of formula III, suitably in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole hydrate, to afford a compound corresponding to formula I wherein  $R^1$  represents  $-COR^{11}$ ; the carbonyl group thereof can then be reduced, for example by treatment with diisobutylaluminium  
 10 hydride, and the required compound of formula I thereby obtained.

The compounds of formula III above wherein T represents CH, U represents  $C-R^2$  and V represents  $N-R^3$ , corresponding to the indole derivatives of formula ID as defined above wherein T represents CH,  $-F-G-$  represents  $-CH_2-N-$  and  $R^1$  is hydrogen, may be prepared by a  
 15 process which comprises reacting a compound of formula IV:



wherein Z and E are as defined above; with a compound of formula V, or a  
 20 carbonyl-protected form thereof:



wherein  $R^2$  and Q are as defined above, and  $R^p$  represents an amino-  
 25 protecting group; followed, where required, by N-alkylation by standard

- 22 -

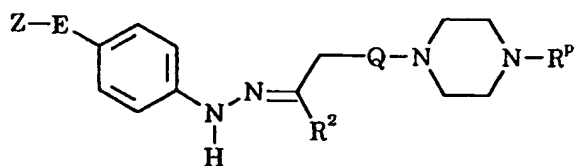
methods to introduce the moiety  $R^3$ ; with subsequent removal of the amino-protecting group  $R^p$ .

The reaction between compounds IV and V, which is an example of the well-known Fischer indole synthesis, is suitably carried out by heating the reagents together under mildly acidic conditions, e.g. 4% sulphuric acid at reflux.

Suitable carbonyl-protected forms of the compounds of formula V include the dimethyl acetal or ketal derivatives.

The protecting group  $R^p$  in the compounds of formula V is suitably a carbamoyl moiety such as t-butoxycarbonyl (BOC), which can conveniently be removed as necessary by treatment under mildly acidic conditions. Indeed, the acidic conditions of the Fischer indole synthesis reaction will generally suffice to remove the BOC group.

The Fischer reaction between compounds IV and V may be carried out in a single step, or may proceed via an initial non-cyclising step at a lower temperature to give an intermediate of formula VI:

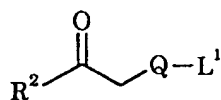


wherein Z, E, Q,  $R^2$  and  $R^p$  are as defined above; followed by cyclisation using a suitable reagent, e.g. a polyphosphate ester.

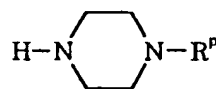
The intermediates of formula V, or carbonyl-protected forms thereof, may be prepared by reacting a compound of formula VII, or a carbonyl-protected form thereof, with a compound of formula VIII:



- 23 -



(VII)



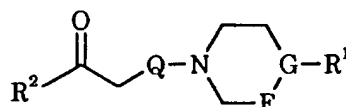
(VIII)

wherein Q, R<sup>2</sup> and R<sup>p</sup> are as defined above, and L<sup>1</sup> represents a suitable leaving group.

5                   The leaving group L<sup>1</sup> is suitably a halogen atom, e.g. chlorine or bromine.

Where L<sup>1</sup> represents a halogen atom, the reaction between compounds VII and VIII is conveniently effected by stirring the reactants under basic conditions in a suitable solvent, for example potassium carbonate in N,N-dimethylformamide, or triethylamine in  
10                   tetrahydrofuran or acetonitrile.

The compounds according to the invention wherein T represents CH, U represents C-R<sup>2</sup> and V represents N-R<sup>3</sup> - i.e. the indole derivatives of formula ID as defined above - may alternatively be prepared  
15                   by a process which comprises reacting a compound of formula IV as defined above with a compound of formula IX, or a carbonyl-protected form thereof:



(IX)

20

wherein Q, F, G, R<sup>1</sup> and R<sup>2</sup> are as defined above; under conditions analogous to those described above for the reaction between compounds IV and V; followed, where required, by N-alkylation by standard methods to introduce the moiety R<sup>3</sup>.

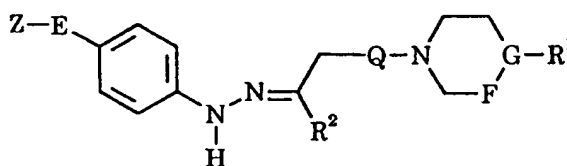
25

As for the compounds of formula V, suitable carbonyl-protected forms of the compounds of formula IX include the dimethyl

- 24 -

acetal or ketal derivatives. Where the alkylene chain Q is substituted by a hydroxy group, this group may condense with the carbonyl moiety in compounds V and IX, whereby the carbonyl moiety is protected in the form of a cyclic hemiacetal.

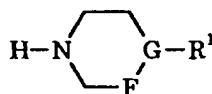
5 As with that between compounds IV and V, the Fischer reaction between compounds IV and IX may be carried out in a single step, or may proceed via an initial non-cyclising step at a lower temperature to give an intermediate of formula X:



(X)

wherein Z, E, Q, F, G, R<sup>1</sup> and R<sup>2</sup> are as defined above; followed by cyclisation using a suitable reagent, e.g. a polyphosphate ester.

15 The intermediates of formula IX, or carbonyl-protected forms thereof, may be prepared by reacting a compound of formula VII as defined above, or a carbonyl-protected form thereof, with a compound of formula XI:

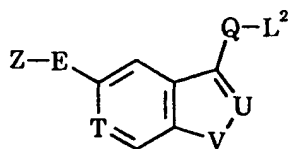


(XI)

20

wherein F, G and R<sup>1</sup> are as defined above; under conditions analogous to those described above for the reaction between compounds VII and VIII.

In an alternative procedure, the compounds of formula III above may be prepared by a process which comprises reacting a compound  
25 of formula VIII as defined above with a compound of formula XII:



(XII)

wherein Z, E, Q, T, U and V are as defined above, and L<sup>2</sup> represents a  
 5 suitable leaving group; followed by removal of the amino-protecting group  
 R<sup>p</sup>.

Similarly, the compounds of formula I as defined above may  
 be prepared by a process which comprises reacting a compound of formula  
 XI as defined above with a compound of formula XII as defined above.

10 The leaving group L<sup>2</sup> is suitably an alkylsulphonyloxy or  
 arylsulphonyloxy group, e.g. methanesulphonyloxy (mesyloxy) or  
 p-toluenesulphonyloxy (tosyloxy).

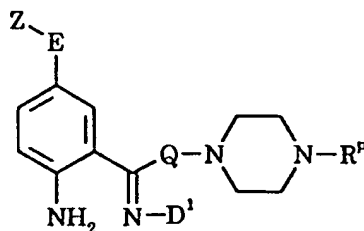
Where L<sup>2</sup> represents an alkylsulphonyloxy or  
 arylsulphonyloxy group, the reaction between compound XII and  
 15 compound VIII or XI is conveniently carried out in a suitable solvent such  
 as 1,2-dimethoxyethane or isopropyl alcohol, typically in the presence of a  
 base such as sodium carbonate or potassium carbonate, optionally with  
 the addition of a catalytic amount of sodium iodide.

In a representative embodiment, the compounds of formula  
 20 XII wherein T and U both represent CH, V represents NH, Q represents a  
 propylene chain and L<sup>2</sup> represents a mesyloxy or tosyloxy group may be  
 prepared by reacting 3,4-dihydro-2H-pyran with a compound of formula  
 IV as defined above or a salt thereof, under a variant of the Fischer  
 reaction conditions as described above for the reaction between  
 25 compounds IV and V; followed by mesylation or tosylation of the 3-  
 hydroxypropyl-indole derivative thereby obtained, typically by treatment  
 with mesyl chloride or tosyl chloride under standard conditions.

- 26 -

The Fischer reaction with 3,4-dihydro-2H-pyran is suitably brought about by heating the hydrazine derivative IV or an acid addition salt thereof, typically the hydrochloride salt, in an inert solvent such as dioxan, advantageously in the presence of a mineral acid such as hydrochloric acid or a Lewis acid such as zinc chloride, at the reflux temperature of the solvent.

In a further procedure, the compounds of formula III above wherein T represents CH, U represents nitrogen and V represents N-R<sup>3</sup>, corresponding to the indazole derivatives of formula IB as defined above wherein -F-G- represents -CH<sub>2</sub>-N- and R<sup>1</sup> is hydrogen, may be prepared by a process which comprises cyclising a compound of formula XIII:

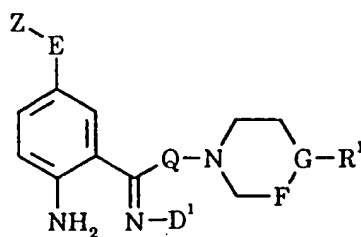


(XIII)

wherein Z, E, Q and R<sup>p</sup> are as defined above, and D<sup>1</sup> represents a readily displaceable group; followed, where required, by N-alkylation by standard methods to introduce the moiety R<sup>3</sup>; with subsequent removal of the amino-protecting group R<sup>p</sup>.

Similarly, the compounds of formula I wherein T represents CH, U represents nitrogen and V represents N-R<sup>3</sup> - i.e. the indazole derivatives of formula IB as defined above - may be prepared by a process which comprises cyclising a compound of formula XIV:

- 27 -

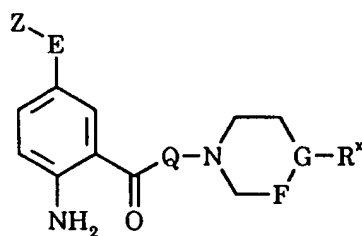


(XIV)

in which Z, E, Q, F, G, R<sup>1</sup> and D<sup>1</sup> are as defined above.

The cyclisation of compounds XIII and XIV is conveniently  
 5 achieved in a suitable organic solvent at an elevated temperature, for  
 example in a mixture of m-xylene and 2,6-lutidine at a temperature in the  
 region of 140°C.

The readily displaceable group D<sup>1</sup> in the compounds of  
 formula XIII and XIV suitably represents a C<sub>1-4</sub> alkanoyloxy group,  
 10 preferably acetoxy. Where D<sup>1</sup> represents acetoxy, the desired compound of  
 formula XIII or XIV may be conveniently prepared by treating a carbonyl  
 compound of formula XV:



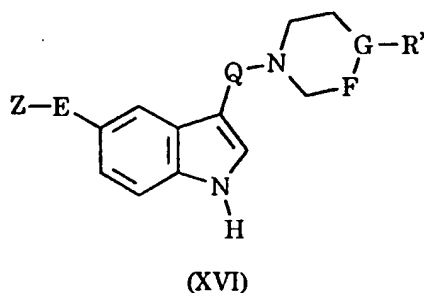
(XV)

15

wherein Z, E, Q, F and G are as defined above, and R<sup>x</sup> corresponds to the  
 group R<sup>1</sup> as defined above, or R<sup>x</sup> represents an amino-protecting group as  
 defined for R<sup>p</sup> when -F-G- represents -CH<sub>2</sub>-N-; or a protected derivative  
 thereof, preferably the N-formyl protected derivative; with hydroxylamine  
 20 hydrochloride, advantageously in pyridine at the reflux temperature of

the solvent; followed by acetylation with acetic anhydride, advantageously in the presence of a catalytic quantity of 4-dimethylaminopyridine, in dichloromethane at room temperature.

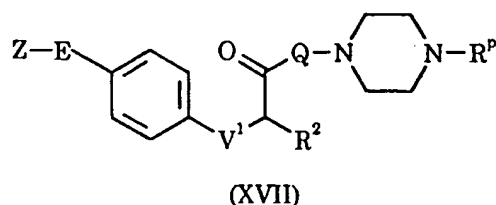
- 5 The N-formyl protected derivatives of the intermediates of formula XV may conveniently be prepared by ozonolysis of the corresponding indole derivative of formula XVI:



- 10 wherein Z, E, Q, F, G and R<sup>x</sup> are as defined above; followed by a reductive work-up, advantageously using dimethylsulphide.

The indole derivatives of formula XVI may be prepared by methods analogous to those described in the accompanying Examples, or by procedures well known from the art.

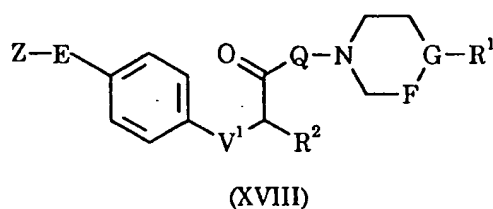
- 15 In a still further procedure, the compounds of formula III above wherein T represents CH, U represents C-R<sup>2</sup> and V represents oxygen or sulphur, corresponding to the benzofuran or benzthiophene derivatives of formula IA wherein V is oxygen or sulphur respectively, -F-G- represents -CH<sub>2</sub>-N- and R<sup>1</sup> is hydrogen, may be prepared by a  
20 process which comprises cyclising a compound of formula XVII:



- 29 -

wherein Z, E, Q, R<sup>2</sup> and R<sup>p</sup> are as defined above, and V<sup>1</sup> represents oxygen or sulphur; followed by removal of the amino-protecting group R<sup>p</sup>.

Similarly, the compounds of formula I wherein T represents CH, U represents C-R<sup>2</sup> and V represents oxygen or sulphur - i.e. the  
 5 benzofuran or benzthiophene derivatives of formula IA above - may be prepared by a process which comprises cyclising a compound of formula XVIII:



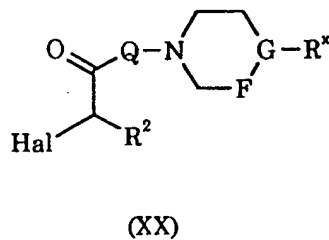
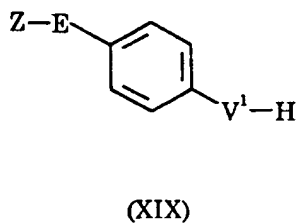
10

wherein Z, E, Q, F, G, R<sup>1</sup>, R<sup>2</sup> and V<sup>1</sup> are as defined above.

The cyclisation of compounds XVII and XVIII is conveniently effected by using polyphosphoric acid or a polyphosphate ester, advantageously at an elevated temperature.

15

The compounds of formula XVII and XVIII may be prepared by reacting a compound of formula XIX with a compound of formula XX:



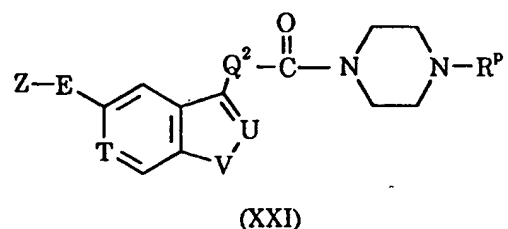
20

wherein Z, E, Q, F, G, R<sup>2</sup>, V<sup>1</sup> and R<sup>x</sup> are as defined above, and Hal represents a halogen atom.

The reaction is conveniently effected in the presence of a base such as sodium hydroxide.

The hydroxy and mercapto derivatives of formula XIX may be prepared by a variety of methods which will be readily apparent to those skilled in the art. One such method is described in EP-A-0497512.

In a yet further procedure, the compounds of formula III  
 5 above may be prepared by a process which comprises reducing a compound of formula XXI:

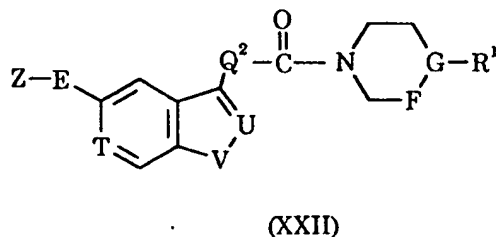


10 wherein Z, E, T, U, V and R<sup>p</sup> are as defined above, and -Q<sup>2</sup>-CH<sub>2</sub>- corresponds to the moiety Q as defined above; with subsequent removal of the amino-protecting group R<sup>p</sup>.

The reaction is suitably carried out by treating the compound of formula XXI with a reducing agent such as lithium aluminium hydride  
 15 in an appropriate solvent, e.g. diethyl ether or tetrahydrofuran, or mixtures thereof.

Similarly, the compounds according to the invention may be prepared by a process which comprises reducing a compound of formula XXII:

20

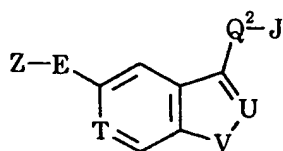


wherein Z, E, T, U, V, F, G, R<sup>1</sup> and Q<sup>2</sup> are as defined above.

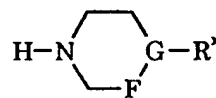


As with compound XXI, the reduction is conveniently effected by treating compound XXII with a reducing agent such as lithium aluminium hydride in an appropriate solvent, e.g. diethyl ether or tetrahydrofuran, or mixtures thereof.

- 5           The compounds of formulae XXI and XXII above may suitably be prepared by reacting a compound of formula XXIII with the appropriate compound of formula XXIV:



(XXIII)



(XXIV)

10

wherein Z, E, T, U, V, F, G, R<sup>x</sup> and Q<sup>2</sup> are as defined above, and J represents a reactive carboxylate moiety.

- Suitable values for the reactive carboxylate moiety J include esters, for example C<sub>1-4</sub> alkyl esters; acid anhydrides, for example mixed  
15   anhydrides with C<sub>1-4</sub> alkanolic acids; acid halides, for example acid chlorides; and acylimidazoles.

- By way of example, the intermediates of formula XXIII above wherein J is an acid chloride moiety may be prepared by treating the corresponding carboxylic acid derivative with thionyl chloride in toluene.  
20   Similarly, the intermediates of formula XXIII wherein J is an acylimidazole moiety may be prepared by treating the corresponding carboxylic acid derivative with 1,1'-carbonyldiimidazole. Alternatively, the reactive carboxylate moiety J may be obtained by treating the corresponding compound wherein J is carboxy with  
25   1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole hydrate, optionally in the presence of triethylamine;

the resulting activated carboxylate intermediate may then suitably be reacted *in situ* with the required compound of formula XXIV.

The hydrazine derivatives of formula IV above may be prepared by methods analogous to those described in EP-A-0438230 and  
5 EP-A-0497512.

Where they are not commercially available, the starting materials of formula VII, VIII, XI, XX, XXIII and XXIV may be prepared by methods analogous to those described in the accompanying Examples, or by standard procedures well known from the art.

10 It will be understood that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula I by techniques known from the art. For example, a compound of formula I wherein -F-G- represents -CH=C- initially obtained may be readily  
15 converted into the corresponding compound wherein -F-G- represents -CH<sub>2</sub>-CH- by conventional catalytic hydrogenation procedures. In addition, a compound of formula I wherein R<sup>1</sup> is benzyl initially obtained may be converted by catalytic hydrogenation to the corresponding compound of formula III, which in turn may be converted into a further  
20 compound of formula I using standard N-alkylation techniques as described above. Furthermore, a compound of formula I initially obtained wherein the R<sup>1</sup> moiety is substituted by nitro or cyano may be converted by catalytic hydrogenation to the corresponding amino- or aminomethyl-substituted compound respectively. Additionally, a compound of formula I  
25 wherein the R<sup>1</sup> moiety is substituted by hydroxy, possibly obtained by lithium aluminium hydride reduction of a precursor alkoxycarbonyl derivative, may be mesylated under standard conditions, and the mesyl group subsequently displaced by an amino moiety by treatment with the desired amine in a sealed tube at an elevated temperature. The amine  
30 derivative resulting from any of these procedures may then, for example, be N-acylated using the appropriate acyl halide, e.g. acetyl chloride; or

aminocarbonylated, using potassium isocyanate, to the corresponding urea derivative; or converted to a 1,2,4-triazol-4-yl derivative using N,N-dimethylformamide azine; or reductively alkylated by treatment with the appropriate aldehyde or ketone in the presence of sodium

5- cyanoborohydride. If desired, the amine derivative may also be carbamoylated by treatment with the requisite alkyl chloroformate. A compound of formula I initially obtained wherein the R<sup>1</sup> moiety is substituted by cyano may be converted, by treatment with sodium azide, to the corresponding tetrazole derivative, which in turn may be alkylated

10 on the tetrazole ring by treatment with an alkyl halide under standard conditions. By way of additional illustration, a compound of formula I initially obtained wherein the R<sup>1</sup> moiety is substituted by an alkoxy carbonyl moiety may be saponified, by treatment with an alkali metal hydroxide, to the corresponding carboxy-substituted compound,

15 which in turn may be converted to an amide derivative by treatment with the appropriate amine, advantageously in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole. Moreover, a compound of formula I wherein R<sup>3</sup> is hydrogen initially obtained may be converted into a compound of formula

20 I wherein R<sup>3</sup> represents C<sub>1-6</sub> alkyl by standard alkylation techniques, for example by treatment with an alkyl iodide, e.g. methyl iodide, typically under basic conditions, e.g. sodium hydride in dimethylformamide, or triethylamine in acetonitrile.

Where the above-described processes for the preparation of

25 the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds

30 may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of

diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid, followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

The compounds in accordance with the present invention potently and selectively bind to the 5-HT<sub>1D $\alpha$</sub>  receptor subtype, inhibit forskolin-stimulated adenylyl cyclase activity, and stimulate [<sup>35</sup>S]-GTP $\gamma$ S binding to membranes from clonal cell lines expressing human cloned receptors.

#### 5-HT<sub>1D $\alpha$</sub> /5-HT<sub>1D $\beta$</sub> Radioligand Binding

Chinese hamster ovary (CHO) clonal cell lines expressing the human 5-HT<sub>1D $\alpha$</sub>  and 5-HT<sub>1D $\beta$</sub>  receptors were harvested in PBS and homogenised in ice cold 50 mM Tris-HCl (pH 7.7 at room temperature) with a Kinematica polytron and centrifuged at 48,000g at 4°C for 11 min. The pellet was then resuspended in 50 mM Tris-HCl followed by a 10 min incubation at 37°C. Finally the tissue was recentrifuged at 48,000g, 4°C for 11 min and the pellet resuspended, in assay buffer (composition in

- 35 -

mM: Tris-HCl 50, pargyline 0.01, CaCl<sub>2</sub> 4; ascorbate 0.1%; pH 7.7 at room temperature) to give the required volume immediately prior to use (0.2 mg protein/ml). Incubations were carried out for 30 min at 37°C in the presence of 0.02-150 nM [<sup>3</sup>H]-5-HT for saturation studies or 2-5 nM [<sup>3</sup>H]-5-HT for displacement studies. The final assay volume was 1 ml. 5-HT (10 μM) was used to define non-specific binding. The reaction was initiated by the addition of membrane and was terminated by rapid filtration through Whatman GF/B filters (presoaked in 0.3% PEI/ 0.5% Triton X) followed by 2 x 4 ml washings with 50 mM Tris-HCl. The radioactive filters were then counted on a LKB beta or a Wallac beta plate counter. Binding parameters were determined by non-linear, least squares regression analysis using an iterative curve fitting routine, from which IC<sub>50</sub> (the molar concentration of compound necessary to inhibit binding by 50%) values could be calculated for each test compound. The IC<sub>50</sub> values for binding to the 5-HT<sub>1Dα</sub> receptor subtype obtained for the compounds of the accompanying Examples were below 50 nM in each case. Furthermore, the compounds of the accompanying Examples were all found to possess a selective affinity for the 5-HT<sub>1Dα</sub> receptor subtype of at least 10-fold relative to the 5-HT<sub>1Dβ</sub> subtype.

20

#### 5-HT<sub>1Dα</sub>/5-HT<sub>1Dβ</sub> Adenylyl Cyclase Assay

Studies were performed essentially as described in *J. Pharmacol. Exp. Ther.*, 1986, 238, 248. CHO clonal cell lines expressing the human cloned 5-HT<sub>1Dα</sub> and 5-HT<sub>1Dβ</sub> receptors were harvested in PBS and homogenised, using a motor driven teflon/glass homogeniser, in ice cold Tris HCl-EGTA buffer (composition in mM: Tris HCl 10, EGTA 1, pH 8.0 at room temperature) and incubated on ice for 30-60 min. The tissue was then centrifuged at 20,000g for 20 min at 4°C, the supernatant discarded and the pellet resuspended in Tris HCl-EDTA buffer

30

(composition in mM: Tris HCl 50, EDTA 5, pH 7.6 at room temperature) just prior to assay. The adenylyl cyclase activity was determined by measuring the conversion of  $\alpha$ -[ $^{33}\text{P}$ ]-ATP to [ $^{33}\text{P}$ ]-cyclic AMP. A 10  $\mu\text{l}$  aliquot of the membrane suspension was incubated, for 10-15 min, in a final volume of 50  $\mu\text{l}$ , at 30°C, with or without forskolin (10  $\mu\text{M}$ ), in the presence or absence of test compound. The incubation buffer consisted of 50 mM Tris HCl (pH 7.6 at room temperature), 100 mM NaCl, 30  $\mu\text{M}$  GTP, 50  $\mu\text{M}$  cyclic AMP, 1 mM dithiothreitol, 1 mM ATP, 5 mM  $\text{MgCl}_2$ , 1 mM EGTA, 1 mM 3-isobutyl-1-methylxanthine, 3.5 mM creatinine phosphate, 0.2 mg/ml creatine phosphokinase, 0.5-1  $\mu\text{Ci}$   $\alpha$ -[ $^{33}\text{P}$ ]-ATP and 1 nCi [ $^3\text{H}$ ]-cyclic AMP. The incubation was initiated by the addition of membrane, following a 5 min preincubation at 30°C, and was terminated by the addition of 100  $\mu\text{l}$  SDS (composition in mM: sodium lauryl sulphate 2%, ATP 45, cyclic AMP 1.3, pH 7.5 at room temperature). The ATP and cyclic AMP were separated on a double column chromatography system (*Anal. Biochem.*, 1974, 58, 541). Functional parameters were determined using a least squares curve fitting programme ALLFIT (*Am. J. Physiol.*, 1978, 235, E97) from which  $E_{\text{max}}$  (maximal effect) and  $\text{EC}_{50}$  (the molar concentration of compound necessary to inhibit the maximal effect by 50%) values were obtained for each test compound. Of those compounds which were tested in this assay, the  $\text{EC}_{50}$  values for the 5-HT $_{1D\alpha}$  receptor obtained for the compounds of the accompanying Examples were below 500 nM in each case. Moreover, the compounds of the accompanying Examples which were tested were all found to possess at least a 10-fold selectivity for the 5-HT $_{1D\alpha}$  receptor subtype relative to the 5-HT $_{1D\beta}$  subtype.

#### 5-HT $_{1D\alpha}$ /5-HT $_{1D\beta}$ GTP $\gamma$ S Binding

Studies were performed essentially as described in *Br. J. Pharmacol.*, 1993, 109, 1120. CHO clonal cell lines expressing the human

- 37 -

cloned 5-HT<sub>1D $\alpha$</sub>  and 5-HT<sub>1D $\beta$</sub>  receptors were harvested in PBS and homogenised using a Kinematica polytron in ice cold 20 mM HEPES containing 10 mM EDTA, pH 7.4 at room temperature. The membranes were then centrifuged at 40,000g, 4°C for 15 min. The pellet was then  
5 resuspended in ice cold 20 mM HEPES containing 0.1 mM EDTA, pH 7.4 at room temperature and recentrifuged at 40,000g, 4°C for 15-25 minutes. The membranes were then resuspended in assay buffer (composition in mM: HEPES 20, NaCl 100, MgCl<sub>2</sub> 10, pargyline 0.01; ascorbate 0.1%; pH 7.4 at room temperature) at a concentration of 40 µg protein/ml for the  
10 5-HT<sub>1D $\alpha$</sub>  receptor transfected cells and 40-50 µg protein/ml for the 5-HT<sub>1D $\beta$</sub>  receptor transfected cells. The membrane suspension was then incubated, in a volume of 1 ml, with GDP (100 µM for 5-HT<sub>1D $\alpha$</sub>  receptor transfected cells, 30 µM for the 5-HT<sub>1D $\beta$</sub>  receptor transfected cells) and test compound at 30°C for 20 min and then transferred to ice for a further 15 min.  
15 [<sup>35</sup>S]-GTP $\gamma$ S was then added at a final concentration of 100 pM and the samples incubated for 30 min at 30°C. The reaction was initiated by the addition of membrane and was terminated by rapid filtration through Whatman GF/B filters and washed with 5 ml water. The radioactive filters were then counted on a LKB beta counter. Functional parameters  
20 were determined by a non-linear, least squares regression analysis using an iterative curve fitting routine, from which E<sub>max</sub> (maximal effect) and EC<sub>50</sub> (the molar concentration of compound necessary to inhibit the maximal effect by 50%) values were obtained for each test compound. Of those compounds which were tested in this assay, the EC<sub>50</sub> values for the  
25 5-HT<sub>1D $\alpha$</sub>  receptor obtained for the compounds of the accompanying Examples were below 500 nM in each case. Moreover, the compounds of the accompanying Examples which were tested were all found to possess at least a 10-fold selectivity for the 5-HT<sub>1D $\alpha$</sub>  receptor subtype relative to the 5-HT<sub>1D $\beta$</sub>  subtype.

EXAMPLE 1

1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(4-(acetamido)benzyl)piperazine. Hydrogen Succinate. Monohydrate

5

1. Intermediate 1: 4'-(1,2,4-Triazol-4-yl)phenylhydrazinea) 4'-Aminoacetanilide

A solution of 4-nitroacetanilide (5.0g, 27.8mmol) in  
10 EtOH/EtOAc (160ml, 1:1), H<sub>2</sub>O (15ml) and 5N HCl (5.6ml, 28.0mmol) was  
hydrogenated over 10% Pd-C (0.50g) at 50 psi for 0.25h. The catalyst was  
removed by filtration through celite and the solvents removed under  
vacuum. The free base was generated by dissolving the product in H<sub>2</sub>O,  
basifying with 2N NaOH and extracting into EtOAc. The combined  
15 extracts were dried (MgSO<sub>4</sub>) and evaporated to give the title-aniline  
(3.75g, 90%).  $\delta$  (250MHz, CDCl<sub>3</sub>/d<sub>4</sub>-MeOH) 2.10 (3H, s, Me); 6.68 (2H, d,  
J = 8.8Hz, Ar-H); 7.27 (2H, d, J = 8.8Hz, Ar-H).

b) 4'-(1,2,4-Triazol-4-yl)acetanilide

20 A mixture of the preceding aniline (3.52g, 23.4mmol), N,N-  
dimethylformamide azine (3.33g, 23.4mmol; *J. Chem. Soc. (C)*, 1967, 1664)  
and p-toluenesulphonic acid monohydrate (0.223g, 1.17mmol), in  
anhydrous toluene (100ml) was heated at reflux for 17h. The beige  
coloured precipitate was filtered off and washed with toluene and CH<sub>2</sub>Cl<sub>2</sub>  
25 and dried under vacuum to give the desired triazole (4.29g, 91%);  $\delta$   
(250MHz, d<sub>4</sub>-MeOH/d<sub>6</sub>-DMSO) 2.14 (3H, s, CH<sub>3</sub>); 7.60 (2H, d, J = 8.8Hz,  
Ar-H); 7.78 (2H, d, J = 8.8Hz, Ar-H); 8.96 (2H, s, Ar-H).

c) 4'-(1,2,4-Triazol-4-yl)phenylaniline

30 A solution of the preceding acetanilide (4.91g, 24.3mmol) in  
5N HCl (100ml) was heated at 125°C for 1.5h. The mixture was cooled to



0°C, basified with concentrated aqueous NaOH solution and extracted with CH<sub>2</sub>Cl<sub>2</sub> (x 5). The combined extracts were dried (MgSO<sub>4</sub>) and evaporated and the residue chromatographed on silica gel, eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (80:8:1), to give the title-*aniline* (2.94g, 76%);  $\delta$  (250MHz, CDCl<sub>3</sub>) 3.80 (2H, s, NH<sub>2</sub>); 6.71 (2H, d, J = 8.8Hz, Ar-H); 7.08 (2H, d, J = 8.8Hz, Ar-H); 8.36 (2H, s, Ar-H).

d) 4'-(1,2,4-Triazol-4-yl)phenylhydrazine

To a solution of the preceding aniline (1.60g, 9.99mmol) in concentrated HCl/H<sub>2</sub>O (23ml and 3ml respectively) was added, at -21°C, a solution of NaNO<sub>2</sub> (0.69g, 9.99mmol) in H<sub>2</sub>O (8ml), at such a rate as to maintain the temperature below -10°C. The mixture was stirred for 0.3h and then filtered rapidly through a sinter, under vacuum. The filtrate was added to a cooled (-20°C) solution of SnCl<sub>2</sub>.2H<sub>2</sub>O (9.02g, 40.0mmol) in concentrated HCl (17ml). The mixture was stirred at -20°C for 0.25h and then at room temperature for 1.25h. The resulting solid was filtered off, washed with Et<sub>2</sub>O and dried under vacuum. The crude product was dissolved in H<sub>2</sub>O, basified with concentrated aqueous NaOH and extracted with EtOAc (x 5). The combined extracts were dried (MgSO<sub>4</sub>) and evaporated to afford the title-product (0.95g, 54%);  $\delta$  (250MHz, CDCl<sub>3</sub>/d<sub>4</sub>-MeOH) 3.98 (3H, br s, NH and NH<sub>2</sub>); 6.97 (2H, d, J = 12.0Hz, Ar-H); 7.25 (2H, d, J = 12.0Hz, Ar-H); 8.48 (2H, s, Ar-H).

2. Intermediate 2: 1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(H)-piperazine. 3.5 Hydrogen Oxalate

1. 5-(4-*tert*-Butyloxycarbonyl)piperazin-1-yl pentanal dimethyl acetal

a) 5-Bromopentanal dimethyl acetal

To a solution of 5-bromovaleryl chloride (50g, 0.251mol) in anhydrous THF (500ml), at -78°C, was added lithium tri-*tert*-

- 40 -

butoxyaluminumhydride (1.0M solution in tetrahydrofuran, 300ml; 0.30mol), keeping the temperature below -70°C. The solution was stirred at -78°C for 5h and then quenched by dropwise addition of 2M hydrochloric acid (350ml). The mixture was warmed to room temperature and stirred for 16h. Diethyl ether (500ml) was added, the aqueous phase separated and extracted further with ether (x 2). The combined extracts were washed with saturated Na<sub>2</sub>CO<sub>3</sub> solution (x 1), water (x 1) and brine (x 2), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to give 5-bromovaleraldehyde (37.5g, 91%). A solution of 5-bromovaleraldehyde (37.5g, 0.227mol) in methanol (250ml) and concentrated sulphuric acid (0.5ml) was stirred at room temperature for 3h. The solvent was removed under vacuum and to the residue was added K<sub>2</sub>CO<sub>3</sub> solution (50ml) and diethyl ether (500ml). The aqueous layer was separated and re-extracted with ether (x 2). The combined extracts were washed with water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The crude product was chromatographed on silica gel eluting with diethyl ether/hexane (1:9) to give the title-acetal (27.5g, 57%).  $\delta$  (250MHz, CDCl<sub>3</sub>) 1.43-1.67 (4H, m, 2 of CH<sub>2</sub>); 1.83-1.94 (2H, m, CH<sub>2</sub>); 3.38 (6H, s, CH(OMe)<sub>2</sub>); 3.42 (2H, t, J = 7Hz, CH<sub>2</sub>Br), 4.37 (1H, t, J = 7Hz, CH(OMe)<sub>2</sub>).

20

b) 5-(4-*tert*-Butyloxycarbonyl)piperazin-1-yl pentanal dimethyl acetal

A mixture of 5-bromovaleraldehyde dimethyl acetal (27.5g, 0.13mol), Na<sub>2</sub>CO<sub>3</sub> (20.7g, 0.195mol), sodium iodide (19.5g, 0.13mol) and *tert*-butyl-1-piperazinecarboxylate (25.5g, 0.137mol), in dimethoxyethane (250ml), was heated at 100°C for 3h. Aluminium foil was wrapped around the vessel to exclude light. The mixture was cooled to room temperature and filtered. The filtrate was evaporated under reduced pressure and then EtOAc (50ml) added and the mixture filtered again to remove inorganic salts. The solvent was removed under vacuum and the residue chromatographed on silica gel eluting with EtOAc to give the title-product (25.7g, 63%).  $\delta$  (250MHz, CDCl<sub>3</sub>) 1.29-1.71 (6H, m, 3 of CH<sub>2</sub>); 1.46 (9H, s,

30

OC(Me)<sub>3</sub>); 2.31-2.39 (6H, m, 3 of CH<sub>2</sub>); 3.32 (6H, s, CH(OMe)<sub>2</sub>); 3.41-3.45 (4H, m, 2 of CH<sub>2</sub>); 4.36 (1H, t, J = 6Hz, CH(OMe)<sub>2</sub>).

2. 1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(H)-piperazine. 3.5

5 Hydrogen Oxalate

A mixture of Intermediate 1 (5.0g, 28.6mmol) and 5-(4-*tert*-butyloxycarbonyl)piperazin-1-yl pentanal dimethylacetal (9.03g, 28.6mmol) in 4% sulphuric acid (150ml) was heated at reflux for 48h. The solution was cooled in an ice-bath, basified with solid K<sub>2</sub>CO<sub>3</sub> and extracted with butan-1-ol (x 3). The solvent was removed under vacuum and azeotroped with hexane (x 2). The crude product was purified by chromatography on silica gel eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (30:8:1) to give the title-indole (3.9g, 44%). The 3.5 hydrogen oxalate salt was prepared using 200mg of free base: mp 90-92°C. (Found: C, 45.97; H, 4.76; N, 13.77. C<sub>17</sub>H<sub>22</sub>N<sub>6</sub>·3.5(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>) requires C, 46.08; H, 4.76; N, 13.43%); δ (360MHz, D<sub>2</sub>O) 2.12-2.24 (2H, m, CH<sub>2</sub>); 2.93 (2H, t, J = 7Hz, CH<sub>2</sub>); 3.46-3.76 (8H, m, 4 of CH<sub>2</sub>); 7.37 (1H, dd, J = 1.9 and 8.7Hz, Ar-H); 7.39 (1H, s, Ar-H); 7.66 (1H, d, J = 8.7, Ar-H); 7.82 (1H, d, J = 1.9Hz, Ar-H); 9.13 (2H, s, Triazole-H).

20

3. 1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(4-(acetamido)benzyl)piperazine. Hydrogen Succinate Monohydrate

To a solution of Intermediate 2 (0.25g, 0.81mmol), glacial acetic acid (0.12g, 2.0mmol) and sodium cyanoborohydride (0.097g, 1.6mmol), in anhydrous methanol (20ml), at 0°C was added a solution of 4-acetamidobenzaldehyde (0.16g, 0.98mmol), in methanol (5ml). The mixture was warmed to room temperature and stirred for 16h. Saturated K<sub>2</sub>CO<sub>3</sub> solution (3ml) was added and the solvent removed under reduced pressure. EtOAc (50ml) and water (10ml) were added to the residue and the aqueous separated and extracted further with EtOAc (x 2). The combined extracts were washed with brine (x 2), dried (Na<sub>2</sub>SO<sub>4</sub>) and

30

evaporated. The crude product was chromatographed on silica gel eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (70:8:1) to give the title-product (0.18g, 50%).

The hydrogen succinate monohydrate salt was prepared: mp 92-94°C;

(Found: C, 60.77; H, 6.65; N, 16.30. C<sub>26</sub>H<sub>31</sub>N<sub>7</sub>O<sub>4</sub>·(C<sub>4</sub>H<sub>6</sub>O<sub>4</sub>)·H<sub>2</sub>O requires C, 60.69; H, 6.62; N, 16.51%); δ (250MHz, D<sub>2</sub>O) 2.10-2.26 (2H, m, CH<sub>2</sub>); 2.28 (3H, s, NHCOMe); 2.60 (4H, s, succinate); 2.82-3.32 (12H, m, 6 of CH<sub>2</sub>); 3.86 (2H, s, CH<sub>2</sub>Ar); 7.35 (1H, dd, J = 2.1 and 8.8Hz, Ar-H); 7.44 (1H, s, Ar-H); 7.46 (2H, d, J = 8.6Hz, Ar-H); 7.54 (2H, d, J = 8.6Hz, Ar-H); 7.69 (1H, d, J = 8.8Hz, Ar-H); 7.78 (1H, d, J = 2.1Hz, Ar-H); 8.89 (2H, s, Triazole-H).

## EXAMPLE 2

1-(4-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]butyl)-4-(4-acetamido)benzyl)piperazine. 2.1 Hydrogen Oxalate. 1.5 Hydrate

1. Intermediate 3: 1-(4-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]butyl)-4-(H)-piperazine

20 a) 6-(4-tert-Butoxycarbonyl)piperazin-1-yl hexanal dimethyl acetal

The title-compound was prepared from 6-bromohexanoyl chloride using the procedure described for Intermediate 2 part 1. δ (360MHz, CDCl<sub>3</sub>) 1.30-1.63 (8H, m, 4 of CH<sub>2</sub>); 1.46 (9H, s, OC(Me)<sub>3</sub>); 2.31-2.40 (6H, m, 3 of CH<sub>2</sub>); 3.31 (6H, s, CH(OMe)<sub>2</sub>); 3.40-3.46 (4H, m, 2 of CH<sub>2</sub>); 4.35 (1H, t, J = 5.7Hz, CH(OMe)<sub>2</sub>).

b) 1-(4-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]butyl)-4-(H)-piperazine

A solution of Intermediate 1 (1.0g, 5.71mmol) and Intermediate 3 (1.9g, 5.76mmol), in 4% H<sub>2</sub>SO<sub>4</sub> (100ml), was heated at reflux for 20h. The mixture was cooled to room temperature, basified with K<sub>2</sub>CO<sub>3</sub> and extracted with *n*-butanol (x 4). The crude product remaining

after removing the solvent under vacuum, and azeotroping with hexane (x 2), was chromatographed on silica gel eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (30:8:1) to give the title-product (0.7g, 38%).  $\delta$  (360MHz, d<sub>6</sub>-DMSO) 1.44-1.52 (2H, m, CH<sub>2</sub>); 1.62-1.70 (2H, m, CH<sub>2</sub>); 2.23-2.27 (6H, m, 3 of CH<sub>2</sub>);  
5 2.62-2.65 (4H, m, 2 of CH<sub>2</sub>); 2.71 (2H, t, J = 7.4Hz, CH<sub>2</sub>); 7.26 (1H, s, Ar-H); 7.29 (1H, dd, J = 2.1 and 8.5Hz, Ar-H); 7.47 (1H, d, J = 8.5Hz, Ar-H); 7.77 (1H, d, J = 2.1Hz, Ar-H); 9.01 (2H, s, Triazole-H); 11.05 (1H, s, NH).

2. 1-(4-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]butyl)-4-(4-  
10 (acetamido)benzyl)piperazine. 2.1 Hydrogen Oxalate. 1.5 Hydrate

Prepared from 1-(4-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]butyl)-4-(H)-piperazine using the general reductive amination procedure described for Example 1. The product was obtained in 59% yield and the 2.1 hydrogen oxalate 1.5 hydrate salt prepared: mp 202-  
15 204°C. (Found: C, 54.70; H, 5.83; N, 14.08. C<sub>27</sub>H<sub>33</sub>N<sub>7</sub>O<sub>2.1</sub>(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>).1.5H<sub>2</sub>O requires C, 54.49; H, 5.89; N, 14.26%);  $\delta$  (360MHz, D<sub>2</sub>O) 1.77 (4H, br s, 2 of CH<sub>2</sub>); 2.17 (3H, s, Me); 2.83 (2H, br s, CH<sub>2</sub>); 3.24 (2H, br s, CH<sub>2</sub>); 3.51 (8H, br s, 4 of CH<sub>2</sub>); 4.35 (2H, s, CH<sub>2</sub>Ar); 7.30 (1H, dd, J = 2.0 and 8.6Hz, Ar-H); 7.33 (1H, s, Ar-H); 7.46 (2H, d, J = 8.5Hz, Ar-H); 7.52 (2H, d, J =  
20 8.5Hz, Ar-H); 7.61 (1H, d, J = 8.6Hz, Ar-H); 7.74 (1H, d, J = 2.0Hz, Ar-H); 8.89 (2H, s, Triazole-H).

EXAMPLE 3

25 1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(2-  
(methoxy)benzyl)piperazine. Trihydrogen Oxalate

The title-compound was prepared from Intermediate 2 and 2-methoxybenzaldehyde using the general procedure described for Example  
30 1. The trihydrogen oxalate salt was prepared: mp 206-208°C. (Found: C, 53.20; H, 5.57; N, 11.88. C<sub>25</sub>H<sub>30</sub>N<sub>6</sub>O<sub>3</sub>(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>) requires C, 53.14; H, 5.18;

N, 11.99%); m/e 431 (M+1)<sup>+</sup>;  $\delta$  (360MHz, D<sub>2</sub>O) 2.10-2.22 (2H, m, CH<sub>2</sub>); 2.91 (2H, t, J = 6.9Hz, CH<sub>2</sub>); 3.27-3.31 (2H, m, CH<sub>2</sub>); 3.63 (8H, br s, 4 of CH<sub>2</sub>); 3.88 (3H, s, OMe); 4.47 (2H, s, CH<sub>2</sub>Ar); 7.05-7.09 (1H, m, Ar-H); 7.14 (1H, dd, J = 1.8 and 8.6Hz, Ar-H); 7.34-7.41 (3H, m, Ar-H); 7.52-7.57 (1H, m, Ar-H); 7.64 (1H, d, J = 8.6Hz, Ar-H); 7.80 (1H, d, J = 1.8Hz, Ar-H); 9.17 (2H, s, Triazole-H).

#### EXAMPLE 4

10 1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(benzyl)piperazine.  
2.25 Hydrogen Maleate

Prepared from Intermediate 2 and benzaldehyde using the general procedure. The 2.25 hydrogen maleate salt was prepared: mp. 15 167-169°C. (Found: C, 58.36; H, 5.55; N, 12.53. C<sub>24</sub>H<sub>28</sub>N<sub>6</sub>.2.25(C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) requires C, 58.31; H, 5.78; N, 12.36%); m/e 401 (M+1)<sup>+</sup>;  $\delta$  (360MHz, d<sub>6</sub>-DMSO) 1.93-2.06 (2H, m, CH<sub>2</sub>); 2.76 (2H, t, J = 7.3Hz, CH<sub>2</sub>); 2.78-3.60 (10H, m, 5 of CH<sub>2</sub>); 3.65 (2H, br s, CH<sub>2</sub>Ph); 6.14 (5H, s, maleate-H); 7.26-7.38 (7H, m, Ar-H); 7.50 (1H, d, J = 8.5Hz, Ar-H); 7.79 (1H, d, J = 2.0Hz, 20 Ar-H); 9.01 (2H, s, Triazole-H); 11.16 (1H, s, NH).

Examples 5-7 inclusive were prepared from Intermediate 2 and the appropriate pyridine carboxaldehyde using the general reductive amination procedure.

25

30

**EXAMPLE 5**

1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(pyridin-3-ylmethyl)piperazine. 6.25 Hydrogen Oxalate 0.8 Hydrate

5

mp: 182-184°C. (Found: C, 43.69; H, 4.29; N, 9.86.C<sub>23</sub>H<sub>27</sub>N<sub>7</sub>. 6.25(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>).0.8H<sub>2</sub>O requires C, 43.57; H, 4.23; N, 10.02%); δ (250MHz, CDCl<sub>3</sub>; free base) 1.87-1.99 (2H, m, CH<sub>2</sub>); 2.44-2.66 (10H, m, 5 of CH<sub>2</sub>); 2.79 (2H, t, J = 7.4Hz, CH<sub>2</sub>); 3.52 (2H, s, CH<sub>2</sub>Ar); 7.14 (1H, dd, J = 2.1 and 8.6Hz, Ar-H), 7.17 (1H, d, J = 2.2Hz, Ar-H); 7.23-7.28 (1H, m, Pyridyl-H); 7.48 (1H, d, J = 8.6Hz, Ar-H); 7.57 (1H, d, J = 2.1Hz, Ar-H); 7.66 (1H, d, J = 1.8 and 7.8Hz, Pyridyl-H); 8.46 (2H, s, Triazole-H); 8.48-8.54 (2H, m, Pyridyl-H); 8.85 (1H, s, NH).

15

**EXAMPLE 6**

1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(pyridin-2-ylmethyl)piperazine. 5.0 Hydrogen Oxalate Monohydrate

20

mp: 124-127°C. (Found: C, 45.41; H, 4.29; N, 11.33. C<sub>23</sub>H<sub>27</sub>N<sub>7</sub>. 5.0(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>).1.0H<sub>2</sub>O requires C, 45.57; H, 4.52; N, 11.27%); δ (360MHz, D<sub>2</sub>O) 2.10-2.24 (2H, m, CH<sub>2</sub>); 2.66-3.64 (12H, m, 6 of CH<sub>2</sub>); 4.12 (2H, s, CH<sub>2</sub>Ar); 7.39 (1H, d, J = 8.7Hz, Ar-H); 7.40 (1H, s, Ar-H); 7.68 (1H, d, J = 8.7Hz, Ar-H); 7.87 (1H, s, Ar-H); 7.94-8.00 (2H, m, Pyridyl-H); 8.51-8.54 (1H, m, Pyridyl-H); 8.70 (1H, d, J = 6.7Hz, Pyridyl-H); 9.48 (2H, s, Triazole-H).

25

30

**EXAMPLE 7**

1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(pyridin-4-ylmethyl)piperazine. 3.2 Hydrogen Oxalate. Hemihydrate

5

mp: 88-90°C. (Found: C, 50.54; H, 4.86; N, 14.33.  $C_{23}H_{27}N_7 \cdot 3.2(C_2H_2O_4) \cdot 0.5H_2O$  requires C, 50.70; H, 4.98; N, 14.13%); m/e 402 (M+1)<sup>+</sup>;  $\delta$  (360MHz,  $d_6$ -DMSO) 1.96-2.10 (2H, m,  $CH_2$ ); 2.44-3.44 (12H, m, 6 of  $CH_2$ ); 3.61 (2H, s,  $CH_2Ar$ ); 7.30-7.36 (4H, m, Ar-H); 7.50 (1H, d, J = 8.6Hz, Ar-H); 7.80 (1H, s, Ar-H); 8.50-8.54 (2H, m, Ar-H); 9.02 (2H, s, Triazole-H); 11.19 (1H, s, NH).

10

**EXAMPLE 8**

1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(4-(amino)benzyl)piperazine. 4.1 Hydrogen Oxalate

15

Reaction of Intermediate 2 with 4-nitrobenzaldehyde under standard reductive amination conditions gave 1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-4-(4-(nitro)benzyl)piperazine in 46% yield.  $PtO_2$  (60mg) was suspended in ethanol (40ml) and stirred under an atmosphere of hydrogen for 0.75h. The preceding nitrobenzyl piperazine (0.33g, 0.74mmol) was then added and the mixture stirred for 2h. The catalyst was removed by filtration through celite, the solvent removed under vacuum and the residue chromatographed on silica gel eluting with  $CH_2Cl_2/MeOH/NH_3$  (70:8:1) to give the title-amino-benzyl piperazine (0.26g, 85%). The 4.1 hydrogen oxalate salt was prepared: mp 150-153°C. (Found: C, 49.04; H, 4.80; N, 12.76.  $C_{24}H_{29}N_7 \cdot 4.1(C_2H_2O_4)$  requires C, 49.28; H, 4.77; N, 12.49%); m/e 416 (M+1)<sup>+</sup>;  $\delta$  (250MHz,  $d_6$ -DMSO; free base) 1.72-1.86 (2H, m,  $CH_2$ ); 2.16-2.44 (10H, m, 5 of  $CH_2$ ); 2.70 (2H, t, J = 7.4Hz,  $CH_2$ ); 3.23 (2H, s,  $CH_2$ ); 4.93 (2H, s,  $NH_2$ ); 6.48 (2H, d, J = 8.4Hz,

20

25

30



Ar-H); 6.89 (2H, d, J = 8.4Hz, Ar-H); 7.27 (1H, s, Ar-H); 7.29 (1H, dd, J = 2.1 and 8.6Hz, Ar-H); 7.47 (1H, d, J = 8.6Hz, Ar-H); 7.78 (1H, d, J = 2.1Hz, Ar-H); 9.02 (2H, s, Triazole-H); 11.07 (1H, s, NH).

- 5 Examples 9-11 inclusive were prepared from 1-(4-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]butyl)-4-(H)-piperazine and the appropriate aromatic aldehyde using the general reductive amination conditions.

### EXAMPLE 9

10

1-(4-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]butyl)-4-(benzyl)piperazine. 2.5 Hydrogen Oxalate

mp: 216-217°C. (Found: C, 56.54; H, 5.61; N, 13.23.

- 15 C<sub>25</sub>H<sub>30</sub>N<sub>6</sub>. 2.5(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>) requires C, 56.33; H, 5.52; N, 13.15%); m/e 415 (M+1)<sup>+</sup>; δ (360MHz, d<sub>6</sub>-DMSO); 1.67 (4H, br s, 2 of CH<sub>2</sub>); 2.46-3.26 (12H, m, 6 of CH<sub>2</sub>); 3.61 (2H, s, CH<sub>2</sub>Ar); 7.26-7.38 (7H, m, Ar-H); 7.48 (1H, d, J = 8.6Hz, Ar-H); 7.78 (1H, d, J = 2.0Hz, Ar-H); 9.01 (2H, s, Triazole-H); 11.13 (1H, s, NH).

20

### EXAMPLE 10

1-(4-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]butyl)-4-(pyridin-2-ylmethyl)piperazine. Sesquioxalate Monohydrate

25

mp: 115-118°C. (Found: C, 56.94; H, 6.13; N, 17.50.

- C<sub>24</sub>H<sub>29</sub>N<sub>7</sub>. 1.5(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>).H<sub>2</sub>O requires C, 57.03; H, 6.03; N, 17.24%); m/e 416 (M+1)<sup>+</sup>; δ (360MHz, d<sub>6</sub>-DMSO) 1.67 (4H, br s, 2 of CH<sub>2</sub>); 2.46-3.26 (12H, m, 6 of CH<sub>2</sub>); 3.71 (2H, s, CH<sub>2</sub>Ar); 7.28-7.32 (3H, m, Ar-H); 7.43 (1H, d, J = 7.8Hz, Pyridyl-H); 7.49 (1H, d, J = 8.6Hz, Ar-H); 7.77-7.82 (2H, m, Ar-H);
- 30

8.49 (1H, d, J = 4.0Hz, Pyridyl-H); 9.01 (2H, s, Triazole-H); 11.14 (1H, s, NH).

### EXAMPLE 11

5

1-(4-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]butyl)-4-(pyridin-3-ylmethyl)piperazine. Sesquioxalate

mp: 110-112°C. (Found: C, 58.80; H, 6.17; N, 18.09.

10 C<sub>24</sub>H<sub>29</sub>N<sub>7</sub>·1.5(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>) requires C, 58.90; H, 5.86; N, 17.81%); m/e 416 (M+1)<sup>+</sup>; δ (360MHz, d<sub>6</sub>-DMSO) 1.67 (4H, br s, 2 of CH<sub>2</sub>); 2.44-3.20 (12H, m, 6 of CH<sub>2</sub>); 3.59 (2H, s, CH<sub>2</sub>Ar); 7.29 (1H, s, Ar-H); 7.30 (1H, dd, J = 2.1 and 8.6Hz, Ar-H); 7.38 (1H, dd, J = 5.0 and 8.1Hz, Pyridyl-H); 7.48 (1H, d, J = 8.7Hz, Ar-H); 7.71 (1H, d, J = 8.1Hz, Pyridyl-H); 7.78 (1H, d, J = 2.1Hz, Ar-H); 8.46-8.52 (2H, m, Pyridyl-H); 9.01 (2H, s, Triazole-H); 11.12 (1H, s, NH).

15

### EXAMPLE 12

20 1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(4-(amino)phenethyl)piperazine. Trihydrogen Oxalate. 1.2 Hydrate

1. 1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(4-(nitro)phenethyl)piperazine

25 A mixture of Intermediate 2 (0.30g, 0.97mmol), K<sub>2</sub>CO<sub>3</sub> (0.27g, 1.94mmol) and *p*-nitrophenethylbromide (0.223g, 0.97mmol), in anhydrous DMF (50ml), was stirred at room temperature for 18h. The mixture was poured into water (100ml) and extracted with EtOAc (x 3). The combined extracts were washed with H<sub>2</sub>O (x 2) and brine (x 2), dried

30 (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The crude product was chromatographed on silica gel eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (90:8:1) to give the title-

piperazine (0.23g, 52%).  $\delta$  (250MHz,  $\text{CDCl}_3$ ) 1.90-2.08 (2H, m,  $\text{CH}_2$ ); 2.40-2.72 (12H, m, 6 of  $\text{CH}_2$ ); 2.81 (2H, t,  $J = 7.4\text{Hz}$ ,  $\text{CH}_2$ ); 2.91 (2H, t,  $J = 7.4\text{Hz}$ ,  $\text{CH}_2$ ); 7.16 (1H, dd,  $J = 2.1$  and  $8.6\text{Hz}$ , Ar-H), 7.19 (1H, s, Ar-H); 7.36 (2H, d,  $J = 8.8\text{Hz}$ , Ar-H); 7.48 (1H, d,  $J = 8.6\text{Hz}$ , Ar-H); 7.57 (1H, d,  $J = 2.1\text{Hz}$ , Ar-H); 8.15 (2H, d,  $J = 8.8\text{Hz}$ , Ar-H); 8.36 (1H, br s, NH); 8.48 (2H, s, Triazole-H).

2. 1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(4-(amino)phenethyl)piperazine. Trihydrogen Oxalate 1.2 Hydrate

10                   Prepared from the preceding 4-(nitro)phenethyl piperazine as described for Example 8. The trihydrogen oxalate 1.2 hydrate salt was prepared: mp 122-125°C. (Found: C, 51.82; H, 5.11; N, 13.22.  $\text{C}_{25}\text{H}_{31}\text{N}_7 \cdot 3.0(\text{C}_2\text{H}_2\text{O}_4) \cdot 1.2\text{H}_2\text{O}$  requires C, 51.62; H, 5.51; N, 13.59%);  $\delta$  (360MHz,  $d_6$ -DMSO) 1.90-2.02 (2H, m,  $\text{CH}_2$ ); 2.62-3.06 (16H, m, 8 of  $\text{CH}_2$ ); 6.52 (2H, d,  $J = 8.3\text{Hz}$ , Ar-H); 6.89 (2H, d,  $J = 8.3\text{Hz}$ , Ar-H); 7.30-7.33 (2H, m, Ar-H); 7.49 (1H, d,  $J = 8.7\text{Hz}$ , Ar-H); 7.79 (1H, d,  $J = 2.0\text{Hz}$ , Ar-H); 9.02 (2H, s, Triazole-H); 11.15 (1H, s, NH).

**EXAMPLE 13**

20                   1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(4-(acetamido)phenethyl)piperazine. 2.75 Hydrogen Oxalate. Hemihydrate

25                   Acetyl chloride (0.020g, 0.26mmol) was added dropwise to a solution of Example 12 (0.10g, 0.23mmol) and  $\text{NEt}_3$  (0.026g, 0.26mmol), in anhydrous dichloromethane (5ml), at 0°C. The solution was warmed to room temperature and stirred for 18h. Dichloromethane (100ml) was added and the solution washed with water (x 2) and brine (x 1). The dichloromethane was dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated and the residue 30 chromatographed on silica gel eluting with  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3$  (90:8:1) to give the title-acetamide (0.078g, 71%). The 2.75 hydrogen oxalate

- 50 -

hemihydrate salt was prepared: mp 217-219°C. (Found: C, 53.74; H, 5.57; N, 13.37.  $C_{27}H_{33}N_7O \cdot 2.75(C_2H_2O_4) \cdot 0.5H_2O$  requires C, 53.60; H, 5.47; N, 13.46%); m/e 472 (M+1)<sup>+</sup>;  $\delta$  (360MHz,  $d_6$ -DMSO) 1.90-2.08 (2H, m, CH<sub>2</sub>); 2.02 (3H, s, NHCOMe); 2.66-3.16 (16H, m, 8 of CH<sub>2</sub>); 7.14-7.16 (2H, d, J = 8.4Hz, Ar-H); 7.33 (2H, br s, Ar-H); 7.47-7.51 (3H, m, Ar-H); 7.79 (1H, s, Ar-H); 9.02 (2H, s, Triazole-H); 9.87 (1H, s, NHCOMe); 11.16 (1H, s, NH).

#### EXAMPLE 14

10 1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(imidazol-2-ylmethyl)piperazine. Trihydrogen Oxalate. Hemihydrate

The title-compound was prepared from Intermediate 2 and imidazole-2-carboxaldehyde using the general reductive amination procedure. The trihydrogen oxalate hemihydrate salt was prepared: mp 133-135°C. (Found: C, 48.25; H, 4.93; N, 16.90.  $C_{21}H_{26}N_8 \cdot 3.0(C_2H_2O_4) \cdot 0.5H_2O$  requires C, 48.43; H, 4.97; N, 16.73%); m/e 391 (M+1)<sup>+</sup>;  $\delta$  (360MHz, D<sub>2</sub>O) 2.04-2.20 (2H, m, CH<sub>2</sub>); 2.50-2.70 (2H, br m, CH<sub>2</sub>); 2.87 (2H, t, J = 7.0Hz, CH<sub>2</sub>); 2.94-3.24 (6H, m, 3 of CH<sub>2</sub>); 3.42-3.60 (2H, m, CH<sub>2</sub>); 3.98 (2H, s, CH<sub>2</sub>); 7.32 (1H, d, J = 8.7Hz, Ar-H); 7.34 (1H, s, Ar-H); 7.38 (2H, s, Imidazole-H); 7.61 (1H, d, J = 8.7Hz, Ar-H); 7.77 (1H, s, Ar-H); 9.12 (2H, s, Triazole-H).

25

30

EXAMPLE 15

1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(3-(acetamido)benzyl)piperazine. Trihydrogen oxalate. Monohydrate

5

1. 1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(3-(amino)benzyl)piperazine

The title-compound was prepared from Intermediate 2 and 3-nitrobenzaldehyde as described for Example 8.

10

2. 1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(3-(acetamido)benzyl)piperazine. Trihydrogen Oxalate. Monohydrate

Prepared from the preceding compound using the procedure described for Example 13. The trihydrogen oxalate monohydrate salt was prepared: mp 208-210°C. (Found: C, 51.36; H, 5.23; N, 13.15).  $C_{26}H_{31}N_7O \cdot 3.0(C_2H_2O_4) \cdot H_2O$  requires C, 51.54; H, 5.27; N, 13.15%;  $\delta$  (360MHz,  $d_6$ -DMSO) 1.96-2.06 (2H, m,  $CH_2$ ); 2.03 (3H, s,  $NHCOMe$ ); 2.50-3.30 (12H, m, 6 of  $CH_2$ ); 3.57 (2H, s,  $CH_2Ar$ ); 6.98 (1H, d,  $J = 7.6Hz$ , Ar-H); 7.25 (1H, dd,  $J = 7.6$  and  $8.5Hz$ , Ar-H); 7.32 (1H, dd,  $J = 1.9$  and  $8.6Hz$ , Ar-H); 7.33 (1H, s, Ar-H); 7.43 (1H, d,  $J = 8.6Hz$ , Ar-H); 7.50 (1H, d,  $J = 8.6Hz$ , Ar-H); 7.61 (1H, s, Ar-H); 7.79 (1H, d,  $J = 1.9Hz$ , Ar-H); 9.01 (2H, s, Triazole-H); 9.94 (1H, s,  $NHCOMe$ ); 11.17 (1H, s, NH).

20

EXAMPLE 16

25

4-(4-Acetamido)benzyl-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine 1.5 Hydrogen Oxalate

1. 3-(5-[1,2,4-Triazol-4-yl]-1H-indol-3-yl)propan-1-ol

30

A solution of 4'-(1,2,4-triazol-4-yl)phenylhydrazine (25g, 143mmol) in dioxan (250ml) was treated with dihydropyran (24g,

286mmol) followed by 1M hydrochloric acid (150ml) and heated at reflux for 18 hours. The reaction mixture was evaporated with toluene then reevaporated. Inorganic solids were removed by treating the residue with a mixture of methanol and acetonitrile. The mother liquors were purified  
5 by column chromatography on silica using dichloromethane:methanol (9:1 → 4:1) as the eluant. The compound was recrystallised from acetonitrile to afford the title compound as a white solid (10.24g, 30%), mp 205-207°C.  $\delta$  (360 MHz,  $d_6$ -DMSO) 1.81 (2H, quintet,  $J=7\text{Hz}$ ,  $\text{CH}_2$ ), 2.75 (2H, t,  $J=8\text{Hz}$ ,  $\text{CH}_2$ ), 3.46 (2H, dt,  $J_1=6\text{Hz}$ ,  $J_2=5\text{Hz}$ ,  $\text{CH}_2$ ), 4.43 (1H, t,  $J=5\text{Hz}$ , OH), 7.26  
10 (1H, d,  $J=2\text{Hz}$ , Ar-H), 7.29 (1H, dd,  $J_1=9\text{Hz}$ ,  $J_2=2\text{Hz}$ , Ar-H), 7.47 (1H, d,  $J=9\text{Hz}$ , Ar-H), 7.77 (1H, d,  $J=2\text{Hz}$ , Ar-H), 9.01 (2H, s, Triazole-H), 11.05 (1H, br s, indole NH). MS,  $\text{CI}^+$ ,  $m/z$  for  $(\text{M}+\text{H})^+=243$ .

15 2. 4-(4-Nitro)benzyl-1,2,5,6-tetrahydropyridine hydrochloride

a) 1-Benzyl-4-(4-nitro)benzylpyridinium bromide

A solution of 4-(4-nitro)benzylpyridine (10.4g, 48mmol) and benzyl bromide (5.8ml, 48mmol) in anhydrous acetone (50ml) was stirred at room temperature for 18 hours. The precipitate was filtered off,  
20 washed with diethyl ether and dried under vacuum to give the desired quaternary salt (16.5g, 90%),  $\delta$  (250MHz,  $d_6$ -DMSO) 4.47 (2H, s,  $\text{CH}_2$ ), 5.82 (2H, s,  $\text{CH}_2$ ), 7.38-7.60 (5H, m, Ar-H), 7.66 (2H, d,  $J=8.8\text{Hz}$ , Ar-H), 8.09 (2H, d,  $J=6.7\text{Hz}$ , Py-H), 8.23 (2H, d,  $J=8.8\text{Hz}$ , Ar-H), 9.15 (2H, d,  $J=6.7\text{Hz}$ , Py-H).

b) 1-Benzyl-4-(4-nitro)benzyl-1,2,5,6-tetrahydropyridine

Sodium borohydride (1.6g, 43mmol) was added dropwise to a cool (0°C) suspension of the foregoing quaternary salt (16.5g, 43mmol) in ethanol (100ml) and water (9ml). The reaction mixture was stirred 18  
30 hours at ambient temperature. The solvent was removed under vacuum and the residue partitioned between water and ethyl acetate. The organic

layer was decanted, dried ( $\text{Na}_2\text{SO}_4$ ), evaporated and the crude product purified by flash chromatography on silica gel eluting with  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  (98/2) to give the title compound (12g, 91%).  $\delta$  (250MHz,  $d_6$ -DMSO) 1.93 (2H, br s,  $\text{CH}_2$ ), 2.45 (2H, dd,  $J_1-J_2=6\text{Hz}$ ,  $\text{CH}_2$ ), 2.87 (2H, br s,  $\text{CH}_2$ ), 3.41 (2H, s,  $\text{CH}_2$ ), 3.49 (2H, s,  $\text{CH}_2$ ), 5.44 (1H, br s, CH), 7.20-7.35 (5H, m, Ar-H), 7.46 (2H, d,  $J=8.6\text{Hz}$ , Ar-H), 8.17 (2H,  $J=8.6\text{Hz}$ , Ar-H).

c) 4-(4-Nitro)benzyl-1,2,5,6-tetrahydropyridine hydrochloride

To a cool ( $-5^\circ\text{C}$ ) solution of the preceding benzyl amine (4.5g, 14.6mmol) in anhydrous dichloromethane was added, dropwise,  $\alpha$ -chloroethylchloroformate (5ml, 43mmol). The solution was stirred whilst warming to room temperature, then stirred overnight. The mixture was evaporated to dryness and the residue was dissolved in methanol (100ml) and heated at reflux for 2 hours. The solvent was evaporated and the solid recrystallised from  $\text{MeOH}/\text{CH}_2\text{Cl}_2$  to give the desired amine (2.3g, 63%).  $\delta$  (250MHz,  $d_6$ -DMSO) 2.14 (2H, br s,  $\text{CH}_2$ ), 3.10 (2H, br d,  $J=5.4\text{Hz}$ ,  $\text{CH}_2$ ), 3.51 (4H, br s, 2 of  $\text{CH}_2$ ), 5.55 (1H, br s, CH), 7.52 (2H, d,  $J=8.6\text{Hz}$ , Ar-H), 8.19 (2H, d,  $J=8.6\text{Hz}$ , Ar-H).

3. 4-(4-Nitro)benzyl-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-1,2,5,6-tetrahydropyridine

To a suspension of 3-(5-[1,2,4-triazol-4-yl]-1H-indol-3-yl)-propan-1-ol (1g, 4.14mmol) in anhydrous tetrahydrofuran (100ml) was added methane sulphonyl chloride (0.2ml, 10mmol) and triethylamine (1.3ml, 10mmol). The mixture was stirred for one hour at ambient temperature then the solvent was evaporated under vacuum and the residue partitioned between 10% aqueous potassium carbonate and dichloromethane. The aqueous was extracted with dichloromethane (3x) then the combined organics were washed with water, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated. The residue was taken into isopropyl alcohol (100ml) then treated with potassium carbonate (1.9g, 13.7mmol), sodium iodide (620mg,

4.14mmol), and 4-(4-nitro)benzyl-1,2,5,6-tetrahydropyridine (3g, 13.7mmol). The mixture was stirred at reflux, in the dark, for 18 hours, then the solvent was removed and the residue partitioned between water and dichloromethane. The organic layer was decanted, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The crude product was purified by flash chromatography on silica eluting with MeOH/CH<sub>2</sub>Cl<sub>2</sub> (5/95) to give the title compound (580mg, 30%).  $\delta$  (250MHz, d<sub>6</sub>-DMSO) 1.75-2.02 (4H, m, 2 of CH<sub>2</sub>), 2.35-2.57 (4H, m, 2 of CH<sub>2</sub>), 2.7 (2H, dd, J<sub>1</sub>=J<sub>2</sub>=7.2Hz, CH<sub>2</sub>), 2.89 (2H, br s, CH<sub>2</sub>), 3.40 (2H, s, CH<sub>2</sub>), 5.43 (1H, br s, CH), 7.23-7.32 (2H, m, Ar-H), 7.38-7.50 (4H, m, Ar-H), 7.77 (1H, d, J=2Hz, Ar-H), 8.17 (2H, d, J=8.6Hz, Ar-H), 9.02 (2H, s, triazol-H), 11.07 (1H, br s, N-H).

4. 4-(4-Amino)benzyl-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine

A suspension of platinum oxide (400mg) in ethanol (50ml) was hydrogenated for 30 minutes under one atmosphere of hydrogen. A solution of the foregoing indole (550mg, 1.24mmol) in ethanol (50ml) was added and the mixture further hydrogenated for 4 hours. The catalyst was removed by filtration and the solvent evaporated under vacuum. The residue was purified by flash chromatography on silica eluting with NH<sub>3</sub>/MeOH/CH<sub>2</sub>Cl<sub>2</sub> (1:10:89) to give the title-product (270mg, 52%).  $\delta$  (250MHz, d<sub>6</sub>-DMSO) 1.01-1.20 (2H, m, CH<sub>2</sub>), 1.21-1.41 (1H, m, CH), 1.42-1.56 (2H, m, CH<sub>2</sub>), 1.66-1.86 (4H, m, 2 of CH<sub>2</sub>), 2.20-2.38 (4H, m, 2 of CH<sub>2</sub>), 2.64-2.75 (2H, m, CH<sub>2</sub>), 2.75-2.89 (2H, m, CH<sub>2</sub>), 4.80 (2H, br s, NH<sub>2</sub>), 6.46 (2H, d, J=8.3Hz, Ar-H), 6.77 (2H, d, J=8.3Hz, Ar-H), 7.24-7.31 (2H, m, Ar-H), 7.46 (1H, d, J=8.6Hz, Ar-H), 7.78 (1H, d, J=2Hz, Ar-H), 9.01 (2H, s, triazol-H), 11.11 (1H, br s, NH).

5. 4-(4-Acetamido)benzyl-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine 1.5 Hydrogen Oxalate



Acetyl chloride (0.019ml, 0.26mmol) in anhydrous dichloromethane (2ml) was added dropwise to a cool (0°C) solution of the preceding aniline (100 mg, 0.24mmol) and triethylamine (0.038ml, 0.26mmol) in anhydrous dichloromethane (10ml). The solution was stirred whilst warming up for 5 hours at room temperature, then quenched with water. The organic layer was decanted, thoroughly washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The residue was purified by flash chromatography on silica eluting with NH<sub>3</sub>/MeOH/CH<sub>2</sub>Cl<sub>2</sub> (1:10:89) to give the title compound (70mg, 64%). The hydrogen oxalate salt had mp 166°C (sintered), (Found: C, 60.52, H, 6.39, N, 14.13. C<sub>27</sub>H<sub>32</sub>N<sub>6</sub>O.1.5(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>).0.25H<sub>2</sub>O requires C, 60.44, H, 6.00, N, 14.10%), δ (360MHz, d<sub>6</sub>-DMSO) 1.30-1.47 (2H, m, CH<sub>2</sub>), 1.62-1.76 (3H, m, CH<sub>2</sub>+CH), 1.96-2.10 (2H, m, CH<sub>2</sub>), 2.01 (3H, s, CH<sub>3</sub>), 2.43-2.54 (2H, m, CH<sub>2</sub>), 2.75 (4H, dd, J<sub>1</sub>=J<sub>2</sub>=7.3Hz, 2 of CH<sub>2</sub>), 2.96-3.10 (2H, m, CH<sub>2</sub>), 3.32-3.48 (2H, m, CH<sub>2</sub>), 7.07 (2H, d, J=8.4Hz, Ar-H), 7.29-7.36 (2H, m, Ar-H), 7.45-7.51 (3H, m, Ar-H), 7.79 (1H, d, J<2Hz, Ar-H), 9.01 (2H, s, triazol-H), 9.86 (1H, s, N-H), 11.18 (1H, s, N-H), MS, Cl<sup>+</sup> m/e for (M+H)<sup>+</sup>=457.

### EXAMPLE 17

#### 4-Benzyl-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-1,2,5,6-tetrahydropyridine 1.85 Hydrogen Oxalate

##### 1. 4-Benzyl-1,2,5,6-tetrahydropyridine

##### a) 1,4-Bis-benzylpyridinium bromide

A solution of 4-benzylpyridine (5.0g, 29.5mmol) in anhydrous acetone (25ml) was treated with benzyl bromide (3.6ml, 30mmol) and stirred at room temperature for 18 hours. The precipitate was collected, washed with diethyl ether then dried to give the quaternary salt as a colourless solid (9.52g, 95%). mp 214-216°C. δ (360MHz, D<sub>2</sub>O) 4.29 (2H,

s, CH<sub>2</sub>), 5.74 (2H, s, CH<sub>2</sub>), 7.30-7.52 (10H, m, Ar-H), 7.84 (2H, d, J=7Hz, Py-H), 8.68 (2H, d, Py-H).

b) 1,4-Bis-benzyl-1,2,5,6-tetrahydropyridine

5                   A solution of the preceding quaternary salt (6.0g, 17.6mmol) in ethanol (30ml) and water (3ml) was cooled to 0°C (ice/salt bath), then treated with sodium borohydride (0.67g, 17.6mmol) in four portions over 15 minutes. The reaction mixture was stirred at 0°C for 2 hours then at room temperature for 4 hours. The mixture was evaporated *in vacuo* then  
10 the residue was partitioned between ethyl acetate (40ml) and water (40ml). The organic layer was separated and the aqueous re-extracted with ethyl acetate (40ml). The combined organics were dried (sodium sulphate) then evaporated *in vacuo* to give the required tetrahydropyridine as an orange gum (3.96g, 85%). R<sub>f</sub> 0.65 in ethyl  
15 acetate on silica plates. δ (360MHz, CDCl<sub>3</sub>) 2.04 (2H, br s, CH<sub>2</sub>), 2.52 (2H, dd, J<sub>1</sub>=J<sub>2</sub>=5Hz, CH<sub>2</sub>), 2.97 (2H, br s, CH<sub>2</sub>), 3.28 (2H, s, CH<sub>2</sub>), 3.56 (2H, s, CH<sub>2</sub>), 5.36 (1H, dd, J<sub>1</sub>=J<sub>2</sub>=1.5Hz, CH<sub>2</sub>), 7.15-7.34 (10H, m, Ar-H).

c) 4-Benzyl-1,2,5,6-tetrahydropyridine

20                   A stirred, cooled (0°C, ice/salt bath) solution of the preceding amine (3.9g, 14.8mmol) in anhydrous dichloromethane (50ml) was treated with α-chloroethylchloroformate (1.9ml, 17.8mmol) then stirred for 4 hours whilst warming to room temperature. The reaction mixture was evaporated to dryness *in vacuo* then the residue was treated with  
25 methanol (50ml) and heated at reflux for 1 hour. The reaction mixture was evaporated to dryness then the residue was partitioned between dichloromethane (50ml) and saturated potassium carbonate solution (50ml). The organic layer was separated, the aqueous re-extracted with dichloromethane (50ml), then the combined organics were dried (sodium  
30 sulphate) and evaporated *in vacuo* to give a red gum (2.9g). The crude product was purified by column chromatography on silica using

dichloromethane/ methanol/ ammonia (20:1:0.1) to afford the title product as a gum (1.0g, 39%),  $\delta$  (360MHz,  $\text{CDCl}_3$ ) 1.98 (2H, br s,  $\text{CH}_2$ ), 2.95 (2H, dd,  $J_1=J_2=6\text{Hz}$ ,  $\text{CH}_2$ ), 3.28 (2H, s,  $\text{CH}_2$ ), 3.32-3.37 (3H, m,  $\text{CH}_2$  and NH), 5.45 (1H, dd,  $J_1=J_2=1\text{Hz}$ , CH), 7.15-7.30 (5H, m, Ar-H).

5

2. 4-Benzyl-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-1,2,5,6-tetrahydropyridine 1.85 Hydrogen Oxalate

The title compound was synthesised from 3-(5-[1,2,4-triazol-4-yl]-1H-indol-3-yl)propan-1-ol and 4-benzyl-1,2,5,6-tetrahydropyridine using the procedure outlined in Example 16, mp  $101^\circ\text{C}$  (Found: C 61.51, H 5.87, N 12.05.  $\text{C}_{25}\text{H}_{27}\text{N}_5 \cdot 1.85 (\text{C}_2\text{H}_2\text{O}_4)$  requires C, 61.11, H, 5.49, N 12.42%),  $\delta$  (360MHz,  $d_6$ -DMSO) 2.02-2.1 (2H, m, 1 of  $\text{CH}_2$ ), 2.16-2.24 (2H, m, 1 of  $\text{CH}_2$ ), 2.42-2.5 (2H, m, 1 of  $\text{CH}_2$ ), 2.55-2.62 (2H, m, 1 of  $\text{CH}_2$ ), 2.77 (2H, t,  $J=8\text{Hz}$ , 1 of  $\text{CH}_2$ ), 3.05-3.15 (2H, m, 1 of  $\text{CH}_2$ ), 3.35 (2H, s, 1 of  $\text{CH}_2$ ), 5.42-5.46 (1H, m, CH), 7.16-7.35 (7H, m, Ar-H), 7.50 (1H, d,  $J=9\text{Hz}$ , Ar-H), 7.8 (1H, d,  $J=2\text{Hz}$ , Ar-H), 9.01 (2H, s, triazole-H), 11.18 (1H, s, indole NH) MS,  $\text{ES}^+$ , m/e for  $(\text{M}+\text{H})^+=398$ .

15

EXAMPLE 18

20

1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-[2-(4-aminocarbonylamino)phenyl]ethyl]piperazine Hemihydrate

To a solution of 1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-4-[2-(4-aminophenyl)ethyl] piperazine (0.25g, 0.58mmol) in  $\text{H}_2\text{O}$  (2ml) and glacial acetic acid (10ml) was added a solution of KCNO (0.096g, 1.17mmol) in  $\text{H}_2\text{O}$  (0.5ml) and the mixture stirred at  $25^\circ\text{C}$  for 22 h. The solution was basified with saturated  $\text{K}_2\text{CO}_3$  solution and extracted with *n*-butanol (3x50ml). The solvent was removed under vacuum and the crude product chromatographed on silica gel eluting with  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3$  (70:8:1) to give the title-product (0.214g, 78%), mp

30

214-216°C. (Found: C, 64.97, H, 6.70, N, 22.90.  $C_{26}H_{32}N_8O \cdot 0.5H_2O$  requires C, 64.85, H, 6.91, N, 23.27%), m/e 473 (M+1)<sup>+</sup>,  $\delta$  (250MHz, d<sub>6</sub>-DMSO) 1.72-1.90 (2H, m, CH<sub>2</sub>), 2.28-2.74 (16H, m, 8 of CH<sub>2</sub>), 5.77 (2H, s, NH<sub>2</sub>), 7.05 (2H, d, J=8.5Hz, Ar-H), 7.25-7.32 (4H, m, Ar-H), 7.47 (1H, d, J=8.6Hz, Ar-H), 7.79 (1H, d, J=2.1Hz, Ar-H), 8.40 (1H, s, NHCONH<sub>2</sub>), 9.03 (2H, s, Ar-H), 11.08 (1H, s, NH).

### EXAMPLE 19

10 1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-[2-(4-cyanophenyl)ethyl]piperazine 2.5 Hydrogen Oxalate

a) 1-(2-(4-Cyanophenyl)ethyl)methane sulphonate

Methane sulphonyl chloride (0.856g, 7.47mmol) was added to  
15 a solution of 2-(4-cyanophenyl)ethanol (1.0g, 6.80mmol) and triethylamine (1.03g, 10.18mmol), in CH<sub>2</sub>Cl<sub>2</sub> (30ml), at +5°C. The mixture was warmed to room temperature and stirred for 2 h before adding H<sub>2</sub>O (15ml), basifying with solid K<sub>2</sub>CO<sub>3</sub> and extracting with CH<sub>2</sub>Cl<sub>2</sub> (x3). The combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to afford the title-  
20 mesylate (1.52g, 100%),  $\delta$  (360MHz, d<sub>6</sub>-DMSO) 3.10 (2H, t, J=6.5Hz, CH<sub>2</sub>-OMs), 3.12 (3H, s, OMs), 4.46 (2H, t, J=6.5Hz, CH<sub>2</sub>), 7.52 (2H, d, J=8.2Hz, Ar-H), 7.80 (2H, d, J=8.2Hz, Ar-H).

b) 1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-[2-(4-cyanophenyl)ethyl]piperazine 2.5 Hydrogen Oxalate

A mixture of 1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-  
4(H)-piperazine (Intermediate 2; 0.5g, 1.61mmol), sodium carbonate (0.26g, 2.45mmol), the preceding mesylate (0.363g, 1.61mmol) and NaI (0.242g, 1.62mmol), in DME (30ml), were heated at 85°C for 16 h. The  
30 remaining solid material was removed by filtration and washed with CH<sub>2</sub>Cl<sub>2</sub>. The solvent was removed under vacuum and the residue

chromatographed on silica gel eluting with  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3$  (70:8:1) to give the title-product (0.20g, 28%). The 2.5 hydrogen oxalate salt was prepared, mp 212-215°C. (Found: C, 55.97, H, 5.31, N, 14.42.  $\text{C}_{26}\text{H}_{29}\text{N}_7 \cdot 2.5(\text{C}_2\text{H}_2\text{O}_4)$  requires C, 56.02, H, 5.16, N, 14.75%), m/e 440 ( $\text{M}+1$ )<sup>+</sup>,  $\delta$  (360MHz,  $d_6$ -DMSO) 1.95-2.08 (2H, m,  $\text{CH}_2$ ), 2.64-3.20 (16H, m, 8 of  $\text{CH}_2$ ), 7.31-7.34 (2H, m, Ar-H), 7.47 (2H, d,  $J=8.3\text{Hz}$ , Ar-H), 7.50 (1H, d,  $J=8.6\text{Hz}$ , Ar-H), 7.76 (2H, d,  $J=8.3\text{Hz}$ , Ar-H), 7.80 (1H, d,  $J=2.0\text{Hz}$ , Ar-H), 9.02 (2H, s, Ar-H), 11.16 (1H, s, NH).

10

**EXAMPLE 20**

1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-[2-(4-(1,2,4-triazol-4-yl)phenyl)ethyl]piperazine 4.0 Hydrogen Oxalate

15

A mixture of 1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-4-[2-(4-aminophenyl)ethyl]piperazine (Example 12; 0.25g, 0.583mmol), N,N-dimethylformamide azine (84mg, 0.583mmol) and *p*-toluene sulphonic acid monohydrate (0.222g, 1.17mmol) in DMF (1.0ml) was heated at 60°C for 20 h. The mixture was cooled to room temperature, basified with saturated  $\text{K}_2\text{CO}_3$  solution and extracted with *n*-butanol (2x30ml). The residue remaining after removal of solvent was chromatographed on silica gel eluting with  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3$  (90:8:1) and the product obtained was rechromatographed on silica gel eluting with diethyl ether/MeOH/ $\text{NH}_3$  (40:8:1) to give the title-compound (84mg, 24%). The 4.0 hydrogen oxalate salt was prepared, mp 200-202°C. (Found: C, 49.94, H, 4.67, N, 14.98.  $\text{C}_{27}\text{H}_{31}\text{N}_9 \cdot 4.0(\text{C}_2\text{H}_2\text{O}_4)$  requires C, 50.09, H, 4.88, N, 15.30%), m/e 482 ( $\text{M}+1$ )<sup>+</sup>,  $\delta$  (360MHz,  $d_6$ -DMSO) 1.92-2.06 (2H, m,  $\text{CH}_2$ ), 2.68-3.18 (16H, m, 8 of  $\text{CH}_2$ ), 7.31-7.33 (2H, m, Ar-H), 7.44 (2H, d,  $J=8.4\text{Hz}$ , Ar-H), 7.50 (1H, d,  $J=8.6\text{Hz}$ , Ar-H), 7.62 (2H, d,  $J=8.4\text{Hz}$ , Ar-H), 7.80 (1H, d,  $J=1.8\text{Hz}$ , Ar-H), 9.02 (2H, s, Ar-H), 9.09 (2H, s, Ar-H), 11.17 (1H, s, NH).

**EXAMPLE 21**

5 1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(4-cyanophenyl)methylpiperazine 1.35 Hydrogen Oxalate 0.25 Hydrate

To a mixture of 1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-4(H)-piperazine (0.155g, 0.5mmol) and K<sub>2</sub>CO<sub>3</sub> (0.138g, 1.0mmol) in anhydrous DMF (5ml) was added 4-cyanobenzyl bromide (0.098g, 0.5mmol) and the mixture heated at 50°C for 0.75 h. The solvent was evaporated and the residue partitioned between ethyl acetate (25ml) and H<sub>2</sub>O (20ml). The organic layer was separated and the aqueous phase extracted with ethyl acetate (2x20ml). The combined organics were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated and the residue chromatographed on silica gel eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH (95:5 -> 90:10) to give the title 4-(cyano)phenylmethyl piperazine (0.19g, 89%). The compound was characterised as the 1.35 hydrogen oxalate 0.25 hydrate salt, mp 144°C (dec.). (Found: C, 60.45, H, 5.89, N, 17.54. C<sub>25</sub>H<sub>27</sub>N<sub>7</sub>·1.35(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>)·0.25 H<sub>2</sub>O requires C, 60.32, H, 5.52, N, 17.78%), m/e 426 (M+1)<sup>+</sup>, δ (360MHz, d<sub>6</sub>-DMSO) 1.94-2.06 (2H, m, CH<sub>2</sub>), 2.42-3.20 (12H, m, 6 of CH<sub>2</sub>), 3.64 (2H, s, CH<sub>2</sub>Ar), 7.30-7.33 (2H, m, Ar-H), 7.49 (1H, d, J=8.8Hz, Ar-H), 7.52 (2H, d, J=8.5Hz, Ar-H), 7.79 (1H, d, J=2.1Hz, Ar-H), 7.81 (2H, d, J=8.5Hz, Ar-H), 9.01 (2H, s, Ar-H), 11.16 (1H, s, NH).

25

**EXAMPLE 22**

1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(2-aminopyridin-5-yl)methylpiperazine 2.3 Hydrogen Oxalate 2.0 Hydrate

30

Triethylamine (175μL, 1.26mmol) was added to a suspension of 1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-4(H)-piperazine

- 61 -

(0.308g, 0.99mmol), 6-aminonicotinic acid (0.142g, 1.03mmol), 1-hydroxybenzotriazole (0.17g, 1.26mmol) and 1-ethyl-3-(3-(dimethylamino)propyl) carbodiimide hydrochloride (0.25g, 1.30mmol), in anhydrous DMF (2.5ml), at room temperature. The mixture was stirred for 24 h and then diluted with water and extracted with <sup>n</sup>BuOH (x3). The combined extracts were evaporated and the residue chromatographed on silica gel eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (90:10:1) to give the desired nicotinamide (0.25g, 59%). Diisobutylaluminium hydride (1.64ml of a 1.0M solution in CH<sub>2</sub>Cl<sub>2</sub>, 1.64mmol) was added to a stirred suspension of the preceding amide (0.141g, 0.33mmol), in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (10ml), at room temperature. After 1.5 h the reaction was cooled to 0°C and quenched with 2N HCl (3ml). The mixture was diluted with water, the CH<sub>2</sub>Cl<sub>2</sub> separated, and the aqueous adjusted to pH,8 with 4N NaOH. The aqueous was extracted with <sup>n</sup>BuOH (x3) and the combined organics evaporated. The residue was taken up in MeOH and evaporated onto silica gel and chromatographed on silica gel eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (80:20:1). The resulting product was rechromatographed on silica gel eluting with Et<sub>2</sub>O/EtOH/H<sub>2</sub>O/NH<sub>3</sub> (60:20:8:1) to give the title-product (44mg, 32%). The 2.3 hydrogen oxalate 2.0 hydrate salt was prepared, mp 189-192°C. (Found: C, 50.61, H, 5.41, N, 16.73. C<sub>23</sub>H<sub>28</sub>N<sub>8</sub>.2.3(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>).2.0H<sub>2</sub>O requires C, 50.26, H, 5.59, N, 16.99%), m/e 417 (M+1)<sup>+</sup>, δ (360MHz, d<sub>6</sub>-DMSO) 1.90-2.04 (2H, m, CH<sub>2</sub>), 2.54-3.18 (12H, m, 6 of CH<sub>2</sub>), 3.52 (2H, s, CH<sub>2</sub>), 6.58 (1H, d, J=8.6Hz, Ar-H), 7.30-7.33 (2H, m, Ar-H), 7.46-7.51 (2H, m, Ar-H), 7.79 (1H, s, Ar-H), 7.83 (1H, s, Ar-H), 9.04 (2H, s, Ar-H), 11.60 (1H, s, NH).

**EXAMPLE 23**

1-(3-[5-(1,2,4-Triazol-1-yl)-1H-indol-3-yl]propyl)-4-benzylpiperazine 2.3  
Hydrogen Oxalate

5

a) 1-(3-[5-(1,2,4-Triazol-1-yl)-1H-indol-3-yl]propyl)-4(H)-piperazine

Prepared from 5-(4-*tert*-butyloxycarbonyl)piperazin-1-yl  
pentanal dimethyl acetal and 4-(1,2,4-triazol-1-yl)phenylhydrazine  
hydrochloride (WO 94/02477) as described for Intermediate 2,  $\delta$  (250MHz,  
10  $d_6$ -DMSO) 1.74-1.86 (2H, m, CH<sub>2</sub>), 2.16-2.36 (6H, m, 3 of CH<sub>2</sub>), 2.58-2.78  
(6H, m, 3 of CH<sub>2</sub>), 4.38 (1H, br s, NH), 7.25 (1H, d, J=2.0Hz, Ar-H), 7.45-  
7.54 (2H, m, Ar-H), 7.93 (1H, d, J=1.6Hz, Ar-H), 8.18 (1H, s, Ar-H), 9.18  
(1H, s, Ar-H), 11.06 (1H, s, NH).

15 b) 1-(3-[5-(1,2,4-Triazol-1-yl)-1H-indol-3-yl]propyl)-4-benzylpiperazine 2.3  
Hydrogen Oxalate

Prepared from 1-(3-[5-(1,2,4-triazol-1-yl)-1H-indol-3-  
yl]propyl)-4(H)-piperazine and benzaldehyde as described for Example 4.  
The 2.3 hydrogen oxalate salt was prepared, mp 210-212°C. (Found: C,  
20 56.49, H, 5.40, N, 13.76. C<sub>24</sub>H<sub>28</sub>N<sub>6</sub>.2.3(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>) requires C, 56.54, H, 5.41,  
N, 13.83%), m/e 401 (M+1)<sup>+</sup>,  $\delta$  1.92-2.06 (2H, m, CH<sub>2</sub>), 2.50-3.06 (12H, m, 6  
of CH<sub>2</sub>), 3.63 (2H, s, CH<sub>2</sub>Ar), 7.24-7.36 (6H, m, Ar-H), 7.48-7.54 (2H, m,  
Ar-H), 7.94 (1H, s, Ar-H), 8.18 (1H, s, Ar-H), 9.16 (1H, s, Ar-H), 11.16 (1H,  
s, NH).

25

30



**EXAMPLE 24**

1-(3-[5-(1,2,4-Triazol-1-yl)-1H-indol-3-yl]propyl)-4-[2-(4-(acetylamino)phenyl)ethyl]piperazine 2.5 Hydrogen Oxalate 0.3 Hydrate

5

Prepared from 1-(3-[5-(1,2,4-triazol-1-yl)-1H-indol-3-yl]propyl)-4(H)-piperazine and *p*-nitrophenethyl bromide using the procedures for Examples 12 and 13. The product was characterised as the 2.5 hydrogen oxalate 0.3 hydrate salt, mp 223-225°C. (Found: C, 54.63, H, 5.61, N, 14.15. C<sub>27</sub>H<sub>33</sub>N<sub>7</sub>O<sub>2.5</sub>(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>).0.3 H<sub>2</sub>O requires C, 54.74, H, 5.54, N, 13.97%), m/e 472 (M+1)<sup>+</sup>, δ (250MHz, d<sub>6</sub>-DMSO) 1.92-2.02 (2H, m, CH<sub>2</sub>), 2.02 (3H, s, Me), 2.68-3.14 (16H, m, 8 of CH<sub>2</sub>), 7.15 (2H, d, J=8.4Hz, Ar-H), 7.31 (1H, s, Ar-H), 7.47-7.55 (4H, m, Ar-H), 7.95 (1H, s, Ar-H), 8.19 (1H, s, Ar-H), 9.17 (1H, s, Ar-H), 9.87 (1H, s, NH), 11.14 (1H, s, NH).

15

**EXAMPLE 25**

1-(3-[5-(1,2,4-Triazol-1-ylmethyl)-1H-indol-3-yl]propyl)-4-benzylpiperazine 2.4 Hydrogen Oxalate 0.1 Diethyl etherate

20

a) 3-(5-[1,2,4-Triazol-1-ylmethyl]-1H-indol-3-yl)propan-1-ol

3,4-Dihydro-2H-pyran (3.9ml, 42.7mmol) was added to a stirred solution of 4-(1,2,4-triazol-1-ylmethyl)phenyl hydrazine (EP 497,512; 4.0g, 21.1mmol) in dioxane/water/5N HCl (38ml/14ml/4.7ml) and stirred at room temperature for 1.75 h. The solution was then refluxed for 1.5 h and the solvent removed under vacuum. The residue was taken up into CH<sub>2</sub>Cl<sub>2</sub> and saturated aqueous K<sub>2</sub>CO<sub>3</sub> solution. The aqueous was separated and further extracted with CH<sub>2</sub>Cl<sub>2</sub> (x4). The combined organic extracts were dried (MgSO<sub>4</sub>) and evaporated and the residue chromatographed on silica gel eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (80:8:1) to give the title-indole (0.919g, 17%), δ (250MHz, CDCl<sub>3</sub>) 1.91-2.03 (2H, m,

30

CH<sub>2</sub>), 2.84 (2H, t, J=7.9Hz, CH<sub>2</sub>), 3.73 (2H, t, J=7.9Hz, CH<sub>2</sub>), 5.43 (2H, s, CH<sub>2</sub>), 7.04 (1H, d, J=2.3Hz, Ar-H), 7.11 (1H, dd, J=2.3 and 8.3Hz, Ar-H), 7.35 (1H, d, J=8.3Hz, Ar-H), 7.58 (1H, s, Ar-H), 7.97 (1H, s, Ar-H), 8.02 (1H, s, Ar-H), 8.18 (1H, s, NH).

5

b) 1-(3-[5-(1,2,4-Triazol-1-ylmethyl)-1H-indol-3-yl]propyl)-4-benzylpiperazine 2.4 Hydrogen Oxalate 0.1 Diethyl etherate

Methanesulphonyl chloride (0.35ml, 4.52mmol) was added dropwise to a stirred solution of triethylamine (0.682ml, 4.89mmol) and the preceding propyl alcohol (0.965g, 3.77mmol), in anhydrous THF (15ml), at -35°C. The mixture was warmed to room temperature and stirred for 16 h. The solvent was removed under vacuum and the residue taken up into CH<sub>2</sub>Cl<sub>2</sub> (50ml) and washed with H<sub>2</sub>O (x2). The CH<sub>2</sub>Cl<sub>2</sub> was dried (MgSO<sub>4</sub>) and evaporated and the residue rapidly flash chromatographed on silica gel eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH (94:6) to give the desired mesylate (0.775g, 62%). K<sub>2</sub>CO<sub>3</sub> (0.901g, 6.5mmol) and N-benzylpiperazine (0.94ml, 5.4mmol) were added successively to a stirred solution of the mesylate (0.727g, 2.17mmol) in IPA (100ml). The mixture was refluxed for 4 h, cooled to room temperature, and the solvent removed under vacuum. The residue was taken up into CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O and the aqueous layer separated and further extracted with CH<sub>2</sub>Cl<sub>2</sub> (x2). The combined extracts were dried (MgSO<sub>4</sub>) and evaporated and the resulting residue was chromatographed on silica gel eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (90:10:1) to give the title-benzylpiperazine (616mg, 68%). The 2.4 hydrogen oxalate 0.1 diethyl etherate salt was prepared, mp 204-206°C. (Found: C, 56.83, H, 5.81, N, 13.14. C<sub>25</sub>H<sub>30</sub>N<sub>6</sub>.2.4(C<sub>2</sub>H<sub>5</sub>O<sub>4</sub>). 0.1(Et<sub>2</sub>O) requires C, 56.85, H, 5.66, N, 13.17%), m/e 415 (M+1)<sup>+</sup>, δ (360MHz, d<sub>6</sub>-DMSO) 1.92-2.04 (2H, m, CH<sub>2</sub>), 2.50-3.30 (12H, m, 6 of CH<sub>2</sub>), 3.64 (2H, s, CH<sub>2</sub>), 5.43 (2H, s, CH<sub>2</sub>), 7.05 (1H, d, J=8.4Hz, Ar-H), 7.19 (1H, s, Ar-H), 7.26-7.36 (6H, m, Ar-H), 7.51 (1H, s, Ar-H), 7.93 (1H, s, Ar-H), 8.60 (1H, s, Ar-H), 10.91 (1H, s, NH).

**EXAMPLE 26**

1-(3-[5-(1,2,4-Triazol-1-ylmethyl)-1H-indol-3-yl]propyl)-4-[2-(4-  
5 (acetylamino)phenyl)ethyl]piperazine 2.5 Hydrogen Oxalate 0.2 Diethyl  
etherate

a) 1-(3-[5-(1,2,4-Triazol-1-ylmethyl)-1H-indol-3-yl]propyl)-4(H)-piperazine

A mixture of 1-(3-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-  
10 yl]propyl)-4-benzylpiperazine (0.53g, 1.28mmol), ammonium formate  
(0.403g, 6.39mmol), 10% Pd-C (0.53g) and MeOH (35ml) was heated at  
66°C for 0.75 h. The catalyst was removed by filtering the reaction  
mixture through celite and washing with EtOH. The combined filtrate  
and washings were evaporated and the residue chromatographed on silica  
15 gel eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (40:8:1) to give the title-N(H)  
piperazine (0.344g, 83%),  $\delta$  (250MHz, CDCl<sub>3</sub>) 1.84-1.96 (2H, m, CH<sub>2</sub>), 2.38-  
2.46 (6H, m, 3 of CH<sub>2</sub>), 2.76 (2H, t, J=7.5Hz, CH<sub>2</sub>), 2.90-2.94 (4H, m, 2 of  
CH<sub>2</sub>), 5.43 (2H, s, CH<sub>2</sub>), 7.03 (1H, s, Ar-H), 7.11 (1H, dd, J=1.7 and 8.2Hz,  
Ar-H), 7.35 (1H, d, J=8.2Hz, Ar-H), 7.57 (1H, s, Ar-H), 7.96 (1H, s, Ar-H),  
20 7.99 (1H, s, Ar-H), 8.22 (1H, br s, NH).

b) 1-(3-[5-(1,2,4-Triazol-1-ylmethyl)-1H-indol-3-yl]propyl)-4-[2-(4-  
(acetylamino)phenyl)ethyl]piperazine 2.5 Hydrogen Oxalate 0.2 Diethyl  
etherate

25 Prepared from 1-(3-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-  
yl]propyl)-4(H)-piperazine and *p*-nitrophenethyl bromide using the  
procedures described for Examples 12 and 13. The product was  
characterised as the 2.5 hydrogen oxalate 0.2 diethyl etherate salt, mp  
208-210°C. (Found: C, 56.08, H, 6.08, N, 13.23. C<sub>28</sub>H<sub>35</sub>N<sub>7</sub>O<sub>2.5</sub>(C<sub>2</sub>H<sub>5</sub>O<sub>4</sub>).  
30 0.2(Et<sub>2</sub>O) requires C, 55.95, H, 5.84, N, 13.51%),  $m/e$  486 (M+1)<sup>+</sup>,  $\delta$   
(360MHz, d<sub>6</sub>-DMSO) 1.88-2.00 (2H, m, CH<sub>2</sub>), 2.02 (3H, s, Me), 2.66-3.12

(16H, m, 8 of CH<sub>2</sub>), 5.44 (2H, s, CH<sub>2</sub>), 7.05 (1H, d, J=8.3Hz, Ar-H), 7.15 (2H, d, J=8.5Hz, Ar-H), 7.18 (1H, s, Ar-H), 7.32 (1H, d, J=8.3Hz, Ar-H), 7.49 (2H, d, J=8.5Hz, Ar-H), 7.52 (1H, s, Ar-H), 7.95 (1H, s, Ar-H), 8.60 (1H, s, Ar-H), 9.87 (1H, s, NH), 10.90 (1H, s, NH).

5

### EXAMPLE 27

1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-[2-(3-(acetylamino)phenyl)ethyl]piperazine. 6.0 Hydrogen Oxalate. 1.5 Hydrate

10

Prepared from 1-(2-(3-(acetylamino)phenyl)ethyl)methane sulphonate and 1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-4(H)-piperazine using the procedure described for Example 19. The compound was characterised as the 6.0 hydrogen oxalate 1.5 hydrate salt

15 (hygroscopic). (Found: C, 45.08, H, 4.91, N, 9.64. C<sub>27</sub>H<sub>33</sub>N<sub>7</sub>O.  
6.0(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>).1.5H<sub>2</sub>O requires C, 45.09, H, 4.65, N, 9.43%), m/e 472 (M+1)<sup>+</sup>,  
δ (360MHz, d<sub>6</sub>-DMSO) 1.90-2.08 (2H, m, CH<sub>2</sub>), 2.02 (3H, s, Me), 2.72-3.16  
(16H, m, 8 of CH<sub>2</sub>), 6.91 (1H, d, J=7.4Hz, Ar-H), 7.18-7.23 (1H, m, Ar-H),  
7.31-7.36 (3H, m, Ar-H), 7.50 (1H, d, J=8.7Hz, Ar-H), 7.51 (1H, s, Ar-H),  
20 7.80 (1H, d, J=1.9Hz, Ar-H), 9.02 (2H, s, Ar-H), 9.89 (1H, s, NH), 11.16  
(1H, s, NH).

### EXAMPLE 28

25 1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-[4-(aminosulphonylphenyl)methyl]piperazine. 1.5 Hydrate. 0.2 Methanol

The title compound was prepared from 1-(4-(aminosulphonyl)phenyl)methyl methane sulphonate and 1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-4(H)-piperazine using the procedure  
30 described for Example 19. The compound was characterised as the 1.5

hydrate which crystallised with 0.2 methanol, mp 166°C, (Found: C, 56.85, H, 6.10, N, 18.71.  $C_{24}H_{29}N_7O_2S \cdot 1.5H_2O \cdot 0.2(MeOH)$  requires C, 56.66, H, 6.44, N, 19.11%), m/e 480 (M+1)<sup>+</sup>.

5

**EXAMPLE 29**

1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(furan-3-ylmethyl)piperazine. 2.25 Hydrogen Oxalate. 1.6 Diethyl etherate

10

Prepared from 1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-4(H)-piperazine and 3-furfuraldehyde using the general reductive amination procedure. The 2.25 hydrogen oxalate salt was prepared which crystallised with diethyl ether, mp 208-210°C, (Found: C, 55.85, H, 6.16, N, 11.46.  $C_{22}H_{26}N_6O \cdot 2.25(C_2H_2O_4) \cdot 1.6(Et_2O)$  requires C, 55.53, H, 6.48, N, 11.80%), m/e 391 (M+1)<sup>+</sup>,  $\delta$  (250MHz,  $d_6$ -DMSO) 1.92-2.08 (2H, m, CH<sub>2</sub>), 2.58-3.24 (12H, m, 6 of CH<sub>2</sub>), 3.54 (2H, s, CH<sub>2</sub>), 6.46 (1H, s, Ar-H), 7.30-7.34 (2H, m, Ar-H), 7.50 (1H, d, J=8.6Hz, Ar-H), 7.64-7.68 (2H, m, Ar-H), 7.80 (1H, d, J=2.0Hz, Ar-H), 9.03 (2H, s, Ar-H), 11.20 (1H, s, NH).

20

**EXAMPLE 30**

1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(furan-2-ylmethyl)piperazine. 1.35 Hydrogen Oxalate

25

Prepared from 1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-4(H)-piperazine and 2-furfuraldehyde as described for Example 1, mp 197-200°C (Found: C, 57.85, H, 5.81, N, 16.51.  $C_{22}H_{26}N_6O \cdot 1.35(C_2H_2O_4)$  requires C, 57.93, H, 5.64, N, 16.41%), m/e 391 (M+1)<sup>+</sup>,  $\delta$  (360MHz,  $d_6$ -DMSO) 1.92-2.06 (2H, m, CH<sub>2</sub>), 2.52-3.20 (12H, m, 6 of CH<sub>2</sub>), 3.60 (2H, s, CH<sub>2</sub>), 6.33 (1H, d, J=3.0Hz, Ar-H), 6.41-6.42 (1H, m, Ar-H),

30

- 68 -

7.30-7.33 (2H, m, Ar-H), 7.49 (1H, d, J=8.9Hz, Ar-H), 7.61 (1H, s, Ar-H), 7.79 (1H, d, J=2.0Hz, Ar-H), 9.01 (2H, s, Ar-H), 11.16 (1H, s, NH).

### EXAMPLE 31

5

1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(thiophen-2-ylmethyl)piperazine. 3.25 Hydrogen Oxalate

Prepared from 1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-4(H)-piperazine and thiophene-2-carboxaldehyde using the  
10 general reductive amination procedure, mp 213-215°C (Found: C, 48.90, H, 4.80, N, 12.01. C<sub>22</sub>H<sub>26</sub>N<sub>6</sub>S.3.25(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>) requires C, 48.96, H, 4.69, N, 12.02%), m/e 407 (M+1)<sup>+</sup>.

15

### EXAMPLE 32

1-Benzyl-4-[(R,S)-2-hydroxy-3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl]piperazine. 2.4 Hydrogen Oxalate

20 a) Ethyl (R,S)-4,5-epoxypentanoate

To a cooled (-5°) and stirred solution of ethyl pent-4-enoate (10g, 78mmol) in dichloromethane (200ml) was added dropwise a solution of m-chloroperoxybenzoic acid (50-55%; 29.5g) in dichloromethane (250ml), over 30 minutes. The mixture was allowed to warm to room  
25 temperature overnight before it was diluted with diethyl ether (700ml) and washed with 2N aqueous sodium hydroxide (150ml), 10% sodium thiosulphate - 10% sodium iodide - 2N sodium hydroxide mixture (1:1:1, 2x80ml) and brine (2x100ml), then dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography (silica gel, dichloromethane to dichloromethane -  
30 diethyl ether, 1:1) of the residue afforded 10g (89%) of the title compound as a colourless liquid.  $\delta$  (360MHz, CDCl<sub>3</sub>) 1.27 (3H, t, J=7.1Hz), 1.79 (1H,

- 69 -

q, J=7.0Hz), 1.97 (1H, m), 2.46 (2H, t, J=7.2Hz), 2.51 (1H, m), 2.77 (1H, m), 2.99 (1H, m), 4.15 (2H, q, J=7.1Hz).

b) (R,S)-5-[(4-Benzylpiperazin-1-yl)methyl]butyrolactone

5                   A solution of the preceding epoxide (3.0g, 20.8mmol) and 4-benzylpiperazine (7.3g, 40.6mmol) in absolute ethanol (40ml) was refluxed, under nitrogen, for 5 hours. The solvent was removed under vacuum and the residue purified by flash chromatography (silica gel, dichloromethane-methanol, 95:5; and silica gel, diethyl ether-ethanol, 10 90:10 to diethyl ether-methanol, 90:10) to give 2.74g of the title compound as a thick pale yellow oil.  $\delta$  (360MHz, CDCl<sub>3</sub>) 1.80-1.94 (1H, m), 2.16-2.28 (1H, m), 2.34-2.60 (12H, m), 3.40-3.44 (2H, m), 4.52-4.62 (1H, m), 7.14-7.28 (5H, m); m/e (ES) 275 (M+1)<sup>+</sup>.

15 c) 1-Benzyl-4-[(R,S)-2-hydroxy-3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl]piperazine. 2.4 Oxalate

To a cooled (-81°C) and stirred solution of the above lactone (2.7g, 9.7mmol) in anhydrous toluene (100ml) was added dropwise, under nitrogen, diisobutylaluminium hydride (1M in toluene; 15.5ml) over 35 20 minutes. After being stirred at -80°C for 2 hours 15 minutes, the reaction was quenched by dropwise addition of methanol (7.8ml) followed by aqueous potassium sodium tartrate (20%, 100ml). Products were extracted with diethyl ether (2x200ml), washed with brine (1x50ml), dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography (silica gel, 25 dichloromethane-methanol, 90:10 to 85:15) gave 2.04g (75.5%) of the intermediate lactol as a colourless oil.

A solution of the above lactol (1.84g, 6.8mmol) and 4'-(1,2,4-triazol-4-yl)phenylhydrazine (1.33g, 7.5mmol) in 4% sulphuric acid (80ml) was stirred at room temperature for 20 minutes and then refluxed for 30 30 hours. After cooling, the mixture was basified with 30% aqueous sodium hydroxide, diluted with ethyl acetate (150ml) and the two-phase mixture

- 70 -

was vigorously stirred for 2 hours. The organic phase was decanted off and the aqueous layer extracted with ethyl acetate (2x200ml). The combined organic solutions were washed with brine (1x50ml), dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography (silica gel, dichloromethane-methanol-ammonia, 92:8:0.8) of the mixture afforded 1.94g (61.5%) of the title compound free base. The oxalate salt was prepared and recrystallised from ethanol-water, mp. 193-196°C. (Found: C, 54.70; H, 5.29; N, 13.40. C<sub>24</sub>H<sub>28</sub>N<sub>6</sub>O x 2.4 C<sub>2</sub>H<sub>2</sub>O<sub>4</sub> requires C, 54.68; H, 5.23; N, 13.29%).  $\delta$  (360MHz, DMSO-d<sub>6</sub>) 2.54-2.76 (4H, m), 2.82-3.24 (8H, m), 3.62 (2H, s), 4.14-4.24 (1H, m), 7.25-7.38 (7H, m), 7.50 (1H, d, J=8.5Hz), 7.81 (1H, d, J=2.0Hz), 8.99 (2H, s), 11.23 (1H, s); m/e (ES) 417 (M+H).

### EXAMPLE 33

1-[4-(Acetylamino)phenethyl]-4-{(R,S)-2-hydroxy-3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperazine. 2.25 Hydrogen Oxalate

#### a) 4-(Acetylamino)phenethyl bromide

A solution of 4-nitrophenethyl bromide (23.8g, 103.6mmol) and acetic anhydride (9.8ml, 103.6mmol) in absolute ethanol (400ml) was hydrogenated over platinum (IV) oxide (2.38g) at 10 psi. The catalyst was removed by filtration and the solvent evaporated under vacuum. The remaining residue was purified by flash chromatography (silica gel, dichloromethane) to give 12.34g of the title compound as a white solid.  $\delta$  (250MHz, CDCl<sub>3</sub>) 2.16 (3H, s), 3.12 (2H, t, J=7.5Hz), 3.53 (2H, t, J=7.5Hz), 7.15 (2H, d, J=8.4Hz), 7.45 (2H, d, J=8.4Hz).



- 71 -

b) 1-[4-(Acetylamino)phenethyl]-4-{(R,S)-2-hydroxy-3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperazine. 2.25 Hydrogen Oxalate

A solution of the product from Example 22 (free base; 1.25g) in absolute ethanol (60ml) was hydrogenated at 48 psi over Pearlman's catalyst (1g) for 18 hours. The catalyst was filtered off, washed with absolute ethanol (3x35ml) and with ethanol-ammonia (30:1; 2x35ml), and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography (silica gel, dichloromethane-methanol-ammonia, 70:30:2) to give 4-{(R,S)-2-hydroxy-3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperazine (788mg, 80%) as a white foam.

A mixture of the above piperazine (270mg, 0.83mmol), 4-(acetylamino)phenethyl bromide (198mg, 0.87mmol) and anhydrous potassium carbonate (114mg, 0.83mmol) in anhydrous dimethylformamide (9ml) was heated at 80°C for 22 hours, under nitrogen. After cooling, water (30ml) and saturated aqueous potassium carbonate (2ml) were added, and products were extracted with ethyl acetate (3x75ml) and with ethyl acetate - butanol (1:1, 1x125ml). The combined organic solutions were concentrated under vacuum and the remaining residue was purified by flash chromatography (silica gel, dichloromethane-methanol-ammonia, 92:8:0.8) to give 221mg (55%) of the title compound free base as a colourless glass. The oxalate salt was prepared from ethanol, mp 210-212°C. (Found: C, 54.55; H, 5.53; N, 14.34.  $C_{27}H_{33}N_7O_2 \times 2.25 C_2H_2O_4$  requires: C, 54.82; H, 5.48; N, 14.21%).  $\delta$  (360MHz, DMSO- $d_6$ ) 2.01 (3H, s), 2.68-3.16 (16H, m), 4.08-4.18 (1H, m), 7.14 (2H, d,  $J=8.5$ Hz), 7.28-7.36 (2H, m), 7.44-7.54 (3H, m), 7.81 (1H, d,  $J=2.0$ Hz), 9.00 (2H, s), 9.86 (1H, s), 11.20 (1H, s); m/e (ES) 488 (M+1)<sup>+</sup>.

**EXAMPLE 34****1-Benzyl-4-[(R,S)-2-(hydroxymethyl)-3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl]piperazine 2.25 Hydrogen Oxalate**

5

**a) 4-Benzyl-1-[(ethoxycarbonyl)acetyl] piperazine**

To a cooled (-20°C) and stirred solution of N-benzylpiperazine (10g, 56.7mmol) and triethylamine (8.7ml, 62.4mmol) in dichloromethane (200ml) was added ethyl malonyl chloride (8.5ml, 66.4mmol) over 10 minutes, under nitrogen. The mixture was allowed to warm to room temperature and it was stirred for 1 hour before water (100ml) and diethyl ether (500ml) were added. The organic phase was decanted off, washed with water (1x70ml), 10% aqueous sodium bicarbonate (1x75ml), brine (1x75ml), then dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography of the residue (silica gel, ethyl acetate - ethanol, 95:5) afforded 9.53g, (58%) of the title compound as a colourless oil.  $\delta$  (360MHz, CDCl<sub>3</sub>), 1.28 (3H, t, J=7.2Hz), 2.48 (4H, br s), 3.45 (2H, s), 3.47 (2H, br s), 3.56 (2H, br s), 3.68 (2H, br s), 4.19 (2H, q, J=7.2Hz), 7.24-7.36 (5H, m); m/e (ES) 291 (M+1)<sup>+</sup>.

20 **b) 4-Benzyl-1-[4-(1,3-dioxolan-2-yl)-2-(ethoxycarbonyl)-butyryl]piperazine**

To a stirred suspension of sodium hydride (60% dispersion in oil, 1.4g) in anhydrous dimethylformamide (50ml) was added dropwise, under nitrogen, a solution of 4-benzyl-1-[(ethoxycarbonyl)acetyl]-piperazine (8.5g, 29.3mmol) in anhydrous dimethylformamide (50ml) over 25 minutes at room temperature. After a further 30 minutes at room temperature, 2-(2-bromoethyl)-1,3-dioxolane (3.6ml, 30.7mmol) was added dropwise over 3 minutes and the resulting yellow solution was stirred for 24 hours. Water (400ml) was added and products were extracted with diethyl ether (3x300ml). The combined ethereal phases were washed with brine (1x150ml), dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography of the residue (silica gel, diethyl ether - ethanol, 95:5) afforded 8g of the

title compound (70%) as a colourless oil,  $\delta$  (360MHz,  $\text{CDCl}_3$ ), 1.25 (3H, t,  $J=7.1\text{Hz}$ ), 1.56-1.78 (2H, m), 2.06 (2H, q,  $J=7.4\text{Hz}$ ), 2.44 (4H, br s), 3.46-3.96 (11H, m), 4.16 (2H, q,  $J=7.1\text{Hz}$ ), 4.86 (1H, t,  $J=4.6\text{Hz}$ ), 7.24-7.36 (5H, m);  $m/e$  (ES) 391 ( $M+1$ )<sup>+</sup>.

5

c) 4-Benzyl-1-[4-(1,3-dioxolan-2-yl)-2-(hydroxymethyl)-butyl]piperazine

To a cooled ( $-30^\circ\text{C}$ ) and stirred solution of lithium aluminium hydride (1M in THF; 16.4ml) in anhydrous tetrahydrofuran (30ml) was added dropwise, *via* cannula, a solution of the product from the preceding step (3.2g, 8.19mmol) in anhydrous tetrahydrofuran (30ml) over 14 minutes, under a nitrogen atmosphere. The resulting clear colourless solution was allowed to warm to room temperature and it was stirred for 4 hours before excess lithium aluminium hydride was destroyed by careful addition of tetrahydrofuran-water (80:20; 25ml) (CAUTION! hydrogen evolution). The precipitated aluminium salts were filtered off, washed with tetrahydrofuran - water (80:20; 2x70ml) and the filtrate was concentrated under vacuum. Flash chromatography of the residue (silica gel, diethyl ether-methanol, 92:8; and silica gel, dichloromethane-methanol, 93:7) afforded 1.96g (71.5%) of the title compound as a colourless oil.  $\delta$  (360MHz,  $\text{CDCl}_3$ ) 1.14-1.24 (2H, m), 1.62-1.72 (2H, m), 1.92-2.06 (1H, m), 2.20-2.90 (10H, m), 3.42-3.56 (3H, m), 3.72-4.00 (5H, m), 4.81 (1H, t,  $J=4.6\text{Hz}$ ), 7.20-7.36 (5H, m);  $m/e$  (ES) 335 ( $M+1$ )<sup>+</sup>.

d) 1-Benzyl-4-[(R,S)-2-(hydroxymethyl)-3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl]piperazine. 2.25 Hydrogen Oxalate

The title compound was prepared from the product of the preceding step and 4'-(1,2,4-triazol-4-yl)phenylhydrazine using a similar method to that described for Example 32 (step 3). The oxalate salt was prepared from absolute ethanol, mp  $188-191^\circ\text{C}$ . (Found: C, 55.94; H, 5.69; N, 13.28.  $\text{C}_{25}\text{H}_{30}\text{N}_6\text{O} \times 2.25 \text{ C}_2\text{H}_2\text{O}_4$  requires: C, 55.96; H, 5.49; N, 13.27%).  $\delta$  (360MHz,  $\text{DMSO}-d_6$ ) 2.14-2.24 (1H, m), 2.64-3.10 (12H, m), 3.39 (1H, dd,

J=10.6 and 6.0Hz), 3.45 (1H, dd, J=10.6 and 4.3Hz), 3.77 (2H, m), 7.26-7.42 (7H, m), 7.49 (1H, d, J=8.6Hz), 7.78 (1H, d, 1.9Hz), 8.99 (2H, s), 11.17 (1H, s); m/e (ES) 431 (M+1)<sup>+</sup>.

5

**EXAMPLE 35**

1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(2-(1-(H)-tetrazol-5-yl)phenyl)methylpiperazine 2.5 Hydrogen Oxalate

10 To a solution of Intermediate 2 (0.155g, 0.5mmol) in anhydrous DMF (5ml) was added K<sub>2</sub>CO<sub>3</sub> (0.138g, 1.0mmol) and α-bromo-*o*-tolunitrile (98mg, 0.5mmol) and the mixture was heated at 50°C for 1h. The solvent was evaporated and the residue partitioned between ethyl acetate (25ml) and water (25ml). The organic layer was separated and the  
15 aqueous phase extracted with ethyl acetate (2x20ml). The combined organics were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated and the residue chromatographed on silica gel, eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH (95:5→90:10) to give the desired *o*-cyanobenzyl piperazine (0.159g, 75%). To a solution of the preceding nitrile (0.156g, 0.36mmol), in N-methyl-2-pyrrolidinone  
20 (5ml) was added triethylamine hydrochloride (75mg, 0.55mmol) and sodium azide (71mg, 1.1mmol) and the mixture heated at 160°C for 6h. After this time, further NaN<sub>3</sub> (36mg, 0.55mmol) and triethylamine hydrochloride (38mg, 0.28mmol) were added, and the mixture heated at 160°C for 10h. The solvent was evaporated and the residue  
25 chromatographed on silica gel eluting with Et<sub>2</sub>O/EtOH/H<sub>2</sub>O (20:20:5) to give the title-tetrazole (56mg, 14%). The 2.5 hydrogen oxalate salt was prepared, mp 150°C (dec.), (Found: C, 51.64, H, 4.99, N, 19.85. C<sub>25</sub>H<sub>28</sub>N<sub>10</sub>. 2.5(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>) requires C, 51.95, H, 4.80, N, 20.19%), m/e 469 (M+1)<sup>+</sup>, δ (360MHz, d<sub>6</sub>-DMSO) 1.85-2.00 (2H, m, CH<sub>2</sub>), 2.66-2.96 (12H, m, 6 of CH<sub>2</sub>),  
30 4.09 (2H, s, CH<sub>2</sub>), 7.26-7.34 (2H, m, Ar-H), 7.46-7.58 (4H, m, Ar-H), 7.78

(1H, s, Ar-H), 7.93 (1H, d, J=7.05Hz, Ar-H), 9.01 (2H, s, Ar-H), 11.12 (1H, s, NH).

### EXAMPLE 36

5

1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(phenethyl)piperazine.  
2.4 Hydrogen Oxalate 0.4 Diethyl etherate

Prepared from Intermediate 2 and phenylacetaldehyde using  
10 the general reductive amination procedure; mp. 193-195 °C. (Found: C, 57.46, H, 6.14; N, 12.97. C<sub>25</sub>H<sub>30</sub>N<sub>6</sub>.2.4(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>). 0.4(Et<sub>2</sub>O) requires C, 57.12; H, 5.92; N, 12.73%); m/e 415 (M+1)<sup>+</sup>; δ (360MHz, d<sub>6</sub>-DMSO) 1.92-2.04 (2H, m, CH<sub>2</sub>), 2.68-3.10 (16H, m, 8 of CH<sub>2</sub>), 7.19-7.34 (7H, m, Ar-H), 7.50 (1H, d, J=8.6Hz, Ar-H), 7.80 (1H, d, J=1.9Hz, Ar-H), 9.02 (2H, s, Ar-H), 11.17  
15 (1H, s, NH).

### EXAMPLE 37

4-Benzyl-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine  
20 Hydrogen Oxalate

A stirred suspension of 3-(5-[1,2,4-triazol-4-yl]-1H-indol-3-yl)-propan-1-ol (300mg, 1.24mmol) in anhydrous tetrahydrofuran (30ml) was treated with methanesulphonyl chloride (192µl, 2.48mmol) and  
25 triethylamine (346µl, 2.48mmol). The reaction mixture was stirred at room temperature for 1.5 hours, filtered, then evaporated. The residue was partitioned between water (50ml) and dichloromethane (50ml). The aqueous was extracted with dichloromethane (50ml) then the combined organics were washed with water (50ml), dried (sodium sulphate) and  
30 evaporated to give the crude mesylate. This mesylate was dissolved in propan-2-ol (70ml), treated with potassium carbonate (515mg, 3.72mmol)

and 4-benzylpiperidine (654 $\mu$ l, 3.72mmol) then stirred whilst heating at reflux for 18 hours. The reaction mixture was evaporated, then the residue partitioned between water (30ml) and dichloromethane (50ml). The organic layer was separated and the aqueous was extracted with  
5 dichloromethane (2x50ml). The combined organics were dried (sodium sulphate) then evaporated to dryness. The crude product was purified by column chromatography on silica using dichloromethane/methanol/ammonia (95:5:0.5) to give the required product free base as a gum (130mg, 26%). The hydrogen oxalate salt had mp 115-117°C. (Found: C, 60.76; H, 6.15; N, 12.77. C<sub>25</sub>H<sub>29</sub>N<sub>5</sub>.1.85C<sub>2</sub>H<sub>2</sub>O<sub>4</sub> requires C, 60.89; H, 5.82;  
10 N, 12.37%);  $\delta$  (360MHz, d<sub>6</sub>-DMSO) 1.30-1.50 (2H, m), 1.65-1.80 (3H, m), 1.98-2.10 (2H, m), 2.48-2.52 (2H, m), 2.75-2.90 (4H, m), 3.00-3.10 (2H, m), 3.35-3.50 (2H, m), 7.16-7.22 (3H, m, Ar-H), 7.27-7.33 (4H, m, Ar-H), 7.50 (1H, d, J=8Hz, Ar-H), 7.80 (1H, s, Ar-H), 9.01 (2H, s, triazole-H), 11.19  
15 (1H, s, indole-H). MS, ES<sup>+</sup>, m/z for (M+H)<sup>+</sup> = 400.

#### EXAMPLES 38 AND 39

4-([2-(1-Methyltetrazol-5-yl)phenyl]methyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperazine. Hydrogen Oxalate and 4-([2-(2-Methyltetrazol-5-yl)phenyl]methyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperazine. 1.45 Hydrogen Oxalate  
20

To a solution of 1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)-4-(2-(1-(H)-tetrazol-5-yl)phenyl)methylpiperazine [Example 35]  
25 (238mg, 0.51mmol) in anhydrous DMF (10ml) was added triethylamine (0.21ml, 1.53mmol) and methyl iodide (95 $\mu$ l, 1.53mmol). The mixture was stirred at room temperature for 20h before more triethylamine (71 $\mu$ l, 0.51mmol) and methyl iodide (32 $\mu$ l, 0.57mmol) were added. The mixture  
30 was stirred for a further 6h, then the solvent was evaporated. The residue was chromatographed on silica gel, eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH

(90:10→80:20) to afford a mixture of the methylated tetrazoles containing a small quantity of impurity. This mixture was re-chromatographed on silica gel, eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (90:10:1) to give a 2:1 mixture of the 2-methyl:1-methyl tetrazoles (76mg, 31%) as a brown foam.

- 5                   The mixture was dissolved (5mg/ml) in 20% CH<sub>3</sub>CN in 0.1% aqueous TFA. 1ml of solution was injected onto a KR100C18 column (250 x 20mm i.d., 5μM) per run, using 20% CH<sub>3</sub>CN in 0.1% aqueous TFA as the mobile phase. Using a flow rate of 20ml/min. and U.V. detection at 230nm, the two isomers were efficiently separated. The fractions  
10 containing each separate isomer were combined and evaporated *in vacuo*.

Isomer A (74mg): Retention time 6.6 min.

Isomer B (40mg): Retention time 7.9 min.

- 15   The TFA salt of each isomer was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (25ml) and Na<sub>2</sub>CO<sub>3</sub> solution (10%, 15ml). The organic phase was separated, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The residue was then chromatographed on silica gel, eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (90:10:1), to afford the 2-methyl isomer (Isomer A) (44mg) as a pale yellow foam and the 1-methyl isomer  
20 (Isomer B) (22mg) as a pale yellow foam.

- The 1.45 hydrogen oxalate salt of the 2-methyl tetrazole was prepared, purity > 99.7%, mp 105°C (dec.), (Found: C, 56.63, H, 5.74, N, 22.91%. C<sub>26</sub>H<sub>30</sub>N<sub>10</sub>.1.45 (C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>) requires C, 56.61, H, 5.41, N, 22.84%),  
m/e 483 (M+1)<sup>+</sup>, δ (360MHz, d<sub>6</sub>-DMSO) 1.92-2.03 (2H, m), 2.42-3.07 (12H,  
25 m), 3.93 (2H, s), 4.44 (3H, s), 7.31-7.33 (2H, m), 7.43-7.55 (3H, m), 7.61 (1H, d, J=7.4Hz), 7.83 (1H, s), 7.87 (1H, d, J=7.5Hz), 9.01 (2H, s), 11.16 (1H, br s).

- The hydrogen oxalate salt of the 1-methyl tetrazole was prepared, purity 96%, mp 128°C(dec.), (Found: C, 59.89, H, 6.09, N, 23.53%. C<sub>26</sub>H<sub>30</sub>N<sub>10</sub>.C<sub>2</sub>H<sub>2</sub>O<sub>4</sub> 0.2(Et<sub>2</sub>O) requires C, 58.88, H, 5.83, N, 23.84%),  
30 m/e 483 (M+1)<sup>+</sup>, δ (360MHz, d<sub>6</sub>-DMSO) 1.90-2.03 (2H, m), 2.24-2.40 (4H,

m), 2.68-2.82 (4H, m), 2.86-3.02 (4H, m), 3.49 (2H, s), 3.91 (3H, s), 7.31-7.33 (2H, m), 7.48-7.62 (5H, m), 7.79 (1H, d, J=1.9Hz), 9.01 (2H, s), 11.16 (1H, br s).

5

**EXAMPLE 40**

4-([2-N-Methylcarboxamidophenyl]methyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperazine. 1.5 Hydrogen Oxalate

10 a) 4-([2-Carbomethoxyphenyl]methyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperazine

To a solution of Intermediate 2 (100mg, 0.32mmol) in anhydrous DMF (5ml) was added K<sub>2</sub>CO<sub>3</sub> (49mg, 0.35mmol) and methyl 2-(bromomethyl)benzoate (81mg, 0.35mmol) and the mixture heated at 70°C  
15 for 2h. The solvent was evaporated and the residue azeotroped with toluene (2x10ml). The residue was chromatographed on silica gel, eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH (90:10) to give the desired ester (106mg, 72%) as a pale yellow foam.  $\delta$  (250MHz, CDCl<sub>3</sub>) 1.84-1.96 (2H, m, CH<sub>2</sub>), 2.39-2.45 (10H, m, 5 of CH<sub>2</sub>), 2.78 (2H, t, J=7.5Hz, CH<sub>2</sub>), 3.74 (2H, s, CH<sub>2</sub>Ar), 3.87  
20 (3H, s, OMe), 7.11-7.15 (2H, m, Ar-H), 7.25-7.41 (3H, m, Ar-H), 7.46 (1H, d, J=8.6Hz, Ar-H), 7.55 (1H, d, J=2Hz, Ar-H), 7.67 (1H, d, J=7.4Hz, Ar-H), 8.46 (2H, s, Ar-H), 8.68 (1H, br s, NH).

25 b) 4-([2-N-Methylcarboxamidophenyl]methyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperazine. 1.5 Hydrogen Oxalate

To a solution of the ester (106mg, 0.23mmol) in methanol/water (10:1, 7ml) was added KOH (39mg, 0.69mmol) and the mixture heated at 60°C for 18h. After this time the solvent was removed *in vacuo* and the residue dissolved in water (10ml). The solution was  
30 adjusted to pH 7 using 1M HCl and the solvent evaporated. The residue



was azeotroped with toluene (2x10ml) and the crude acid used in the subsequent reaction without further purification.

To a solution of the resultant acid in anhydrous DMF (5ml) was added triethylamine (51 $\mu$ L, 0.37mmol), 1-hydroxybenzotriazole (37mg, 0.28mmol), methylamine (191 $\mu$ L of a 8.0M solution in THF, 1.5mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (71mg, 0.37mmol). The mixture was stirred at room temperature for 3 days, before the solvent was evaporated. The residue was azeotroped with toluene (2x10ml) and then partitioned between dichloromethane (20ml) and water (20ml). The organic layer was separated, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The residue was chromatographed on silica gel, eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (90:10:1) to give the title amide (40mg, 38%) as a colourless oil. The 1.5 hydrogen oxalate salt was prepared, mp 150°C, (Found C, 58.48, H, 6.00, N, 16.77%. C<sub>26</sub>H<sub>31</sub>N<sub>7</sub>O.1.5(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>) requires C, 58.77, H, 5.78, N, 16.54%), m/e 458 (M+1)<sup>+</sup>,  $\delta$  (360MHz, d<sub>6</sub>-DMSO) 1.98-2.06 (2H, m), 2.48-3.20 (15H, m), 3.68 (2H, s), 7.30-7.51 (7H, m), 7.80 (1H, d, J=1.9Hz), 8.58 91H, br s), 9.01 (2H, s), 11.17 (1H, br s).

20

#### EXAMPLE 41

4-([2-N,N-Dimethylaminomethylphenyl]methyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperazine. 1.5 Hydrogen Oxalate

25

A solution of the nitrile (75mg, 0.18mmol), (prepared as described in Example 35) in ethanol (20ml) was hydrogenated at 40psi, in the presence of platinum IV oxide (100mg) and 1M HCl (0.35ml) for 3 h. After this time the catalyst was filtered off and the filtrate evaporated. The residue was partitioned between dichloromethane (2x20ml) and 1M NaOH (20ml). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated *in vacuo*. The residue was chromatographed on silica gel,

30

eluting with  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3$  (40:8:1), to give the benzylamine (38mg, 51%) as a colourless foam.

To a stirred solution of the benzylamine (38mg, 0.09mmol) at  $0^\circ\text{C}$  in methanol (10ml) was added sodium cyanoborohydride (17mg, 0.27mmol), acetic acid (25 $\mu\text{l}$ , 0.44mmol) and formaldehyde (17 $\mu\text{l}$  of a 38% (w/v) aqueous solution). The cooling bath was removed and the mixture stirred at room temperature for 3h. After this time sat.  $\text{K}_2\text{CO}_3$  solution (5ml) was added and the mixture stirred for 15min. The solvents were then evaporated and the residue partitioned between dichloromethane (20ml) and water (20ml). The organic phase was separated, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated. The residue was chromatographed on silica gel, eluting with  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3$  (40:8:1), to give the title amine (28mg, 69%) as a colourless foam. The 1.5 hydrogen oxalate salt was prepared, mp  $161^\circ\text{C}$ , (Found: C, 59.80, H, 6.82, N, 16.18%.  $\text{C}_{27}\text{H}_{35}\text{N}_7 \cdot 1.5(\text{C}_2\text{H}_2\text{O}_4) \cdot 0.5(\text{H}_2\text{O})$  requires C, 59.89, H, 6.53, N, 16.30%), m/e 458 ( $\text{M}+1$ )<sup>+</sup>,  $\delta$  (360MHz,  $\text{d}_6$ -DMSO) 1.82-1.93 (2H, m), 2.50-2.80 (18H, m), 3.86 (2H, s), 4.24 (2H, s), 7.28-7.33 (2H, m), 7.46-7.50 (5H, m), 7.78 (1H, s), 9.02 (2H, s), 11.13 (1H, br s).

20

#### EXAMPLE 42

4-(But-3-enyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperazine.  
Hydrogen Oxalate

25

To a solution of Intermediate 2 (100mg, 0.32mmol) in anhydrous DMF (5ml) was added  $\text{K}_2\text{CO}_3$  (53mg, 0.39mmol) and 4-bromo-1-butene (33 $\mu\text{l}$ , 0.32mmol). The mixture was heated at  $50^\circ\text{C}$  for 45min and then at  $70^\circ\text{C}$  for 2.5h. More bromide (16 $\mu\text{l}$ , 0.16mmol) was added and the mixture heated at  $70^\circ\text{C}$  for a further 1 h. The solvent was evaporated and the residue partitioned between  $\text{CH}_2\text{Cl}_2$  (3x20ml) and water (20ml). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated. The

30

residue was chromatographed on silica gel, eluting with  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3$  (93:7:1) to give the piperazine (63mg, 54%) as a pale yellow foam. The hydrogen oxalate salt was prepared, mp  $126^\circ\text{C}$  (dec.), (Found: C, 57.75, H, 6.85, N, 17.59%.  $\text{C}_{21}\text{H}_{28}\text{N}_6 \cdot 1.0(\text{C}_2\text{H}_2\text{O}_4) \cdot 1.3(\text{H}_2\text{O})$  requires C, 57.80, H, 6.88, N, 17.58%),  $m/e$  365 ( $M+1$ )<sup>+</sup>,  $\delta$  (360MHz,  $d_6$ -DMSO) 1.90-2.01 (2H, m), 2.23-2.30 (2H, m), 2.57-3.10 (14H, m), 5.02 (1H, d,  $J=10.3\text{Hz}$ ), 5.09 (1H, dd,  $J=17$  and  $2\text{Hz}$ ), 5.74-5.82 (1H, m), 7.29-7.33 (2H, m), 7.49 (1H, d,  $J=8.5\text{Hz}$ ), 7.79 (1H, d,  $J=2.0\text{Hz}$ ), 9.02 (2H, s), 11.16 (1H, br s).

#### EXAMPLE 43

4-(3-Methyl-but-2-enyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperazine. 1.3 Hydrogen Oxalate

To a solution of Intermediate 2 (200mg, 0.65mmol) in anhydrous DMF (5ml) was added  $\text{K}_2\text{CO}_3$  (107mg, 0.78mmol) and 4-bromo-2-methyl-2-butene (82 $\mu\text{l}$ , 0.78mmol). The mixture was heated at  $50^\circ\text{C}$  for 45 min then the solvent was evaporated and the residue partitioned between  $\text{CH}_2\text{Cl}_2$  (25ml) and water (25ml). The organic layer was separated and the aqueous phase washed further with  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3$  (90:10:1) to give the title compound (75mg, 30%) as a pale yellow gum. The 1.3 hydrogen oxalate salt was prepared, mp.  $137^\circ\text{C}$  (dec.), (Found: C, 59.62, H, 6.86, N, 17.18%.  $\text{C}_{22}\text{H}_{30}\text{N}_6 \cdot 1.3(\text{C}_2\text{H}_2\text{O}_4)$  requires C, 59.62, H, 6.63, N, 16.96%),  $m/e$  379 ( $M+1$ )<sup>+</sup>,  $\delta$  (360MHz,  $d_6$ -DMSO) 1.65 (3H, s), 1.73 (3H, s), 1.82-1.96 (2H, m) 2.51-2.90 (12H, m), 3.18 (2H, d,  $J=6.8\text{Hz}$ ), 5.17-5.24 (1H, br t,  $J=6.8\text{Hz}$ ), 7.30-7.33 (2H, m), 7.49 (1H, d,  $J=8.6\text{Hz}$ ), 7.79 (1H, s), 9.03 (2H, s), 11.13 (1H, br s).

**EXAMPLE 44**

4-(Prop-2-enyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperazine.

1.3 Hydrogen Oxalate

- 5 To a solution of Intermediate 2 (200mg, 0.65mmol) in anhydrous DMF (5ml) was added K<sub>2</sub>CO<sub>3</sub> (78mg, 1.29mmol) and allyl bromide (61μl, 0.71mmol). The mixture was heated at 40°C for 1.3h then more bromide (11μl, 0.13mmol) was added and heating continued for a
- 10 further 45min. After this time the mixture was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (40ml) and water (30ml). The organic layer was separated and the aqueous phase extracted with CH<sub>2</sub>Cl<sub>2</sub> (30ml). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated and the residue
- 15 The title compound (46mg, 20%) was isolated as a pale yellow foam. The 1.5 hydrogen oxalate salt was prepared, mp 98°C (dec.), (Found: C, 56.94, H, 6.07, N, 17.49%. C<sub>20</sub>H<sub>26</sub>N<sub>6</sub>. 1.5(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>) requires C, 56.90, H, 6.02, N, 17.31%), m/e 351 (M+1)<sup>+</sup>, δ (360MHz, d<sub>6</sub>-DMSO) 1.91-2.06 (2H, m), 2.56-3.20 (14H, m), 5.23-5.30 (2H, m), 5.73-5.90 (1H, m), 7.31-7.35 (2H, m),
- 20 7.50 (1H, d, J=8.7Hz), 7.80 (1H, s), 9.03 (2H, s), 11.18 (1H, br s).

**EXAMPLE 45**

4-Propargyl-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperazine. 1.4

25 Hydrogen Oxalate

- To a solution of Intermediate 2 (100mg, 0.32mmol) in anhydrous DMF (5ml) was added K<sub>2</sub>CO<sub>3</sub> (53mg, 0.39mmol) and propargyl bromide (39μl, 0.35mmol). The mixture was heated at 50°C for 1h then
- 30 the solvent was evaporated and the residue chromatographed on silica gel, eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (93:7:1) to give the title compound (61mg,

54%) as a pale yellow foam. The 1.4 hydrogen oxalate salt was prepared, mp 110°C, (Found: C, 57.63, H, 6.03, N, 17.51%.  $C_{20}H_{24}N_6 \cdot 1.4(C_2H_2O_4)$  requires C, 57.71, H, 5.69, N, 17.71%), m/e 349 (M+1)<sup>+</sup>,  $\delta$  (360MHz,  $d_6$ -DMSO) 1.94-2.06 (2H, m), 2.74-2.80 (6H, m), 2.86-3.27 (7H, m), 3.32-3.43 (2H, m), 7.30-7.36 (2H, m), 7.49 (1H, d, J=8.5Hz), 7.80 (1H, s), 9.02 (2H, s), 11.18 (1H, br s).

#### EXAMPLE 46

10 4-((R,S)-1-(Phenyl)carboxamidomethyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperazine. 1.5 Hydrogen Oxalate

a) 4-((R,S)-1-(Phenyl)carbomethoxymethyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperazine

15 To a solution of Intermediate 2 (200mg, 0.64mmol) in anhydrous DMF (5ml) was added  $K_2CO_3$  (98mg, 0.71mmol) and methyl  $\alpha$ -bromophenyl acetate (112 $\mu$ l, 0.71mmol), and the mixture heated at 60°C for 90min. The solvent was evaporated and the residue chromatographed on silica gel, eluting with  $CH_2Cl_2$ /MeOH (93:7) to give the  $\alpha$ -methyl ester  
20 (205mg, 70%) as a cream foam.  $\delta$  1.92-2.02 (2H, m), 2.42-2.70 (10H, m), 2.78 (2H, t, J=7.4Hz), 3.67 (3H, s), 4.00 (1H, s), 7.10-7.18 (2H, m), 7.27-7.41 (5H, m), 7.48 (1H, d, J=8.5Hz), 7.54 (1H, d, J=2Hz), 8.47 (2H, s), 9.05 (1H, br s).

25 b) 4-((R,S)-1-(Phenyl)carboxamidomethyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperazine

A solution of the ester (205mg, 0.45mmol) in methanol/water (7ml (6:1)) was heated at 60°C for 10h in the presence of sodium hydroxide (36mg, 0.89mmol). The solvent was evaporated and the residue dissolved  
30 in water. 1M HCl was added to adjust the pH to 7 then the water was removed *in vacuo*. The residue was azeotropered with toluene (2x7ml) and

the crude acid used in the subsequent reaction without further purification.

To a solution of the crude acid in anhydrous DMF (7ml) was added triethylamine (77 $\mu$ l, 0.55mmol), 1-hydroxybenzotriazole (72mg, 0.54mmol), ammonia (573 $\mu$ l of a 2M solution in MeOH, 1.1mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (106mg, 0.55mmol). The mixture was stirred at room temperature for 24h, before removal of the solvent *in vacuo*. The residue was azeotroped with toluene (2x10ml) and the residue chromatographed on silica eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (90:10:1), to afford the title amide (158mg, 80%) as a colourless foam. The 1.5 hydrogen oxalate salt was prepared, mp 153°C, (Found: C, 58.18, H, 5.69, N, 17.31%. C<sub>25</sub>H<sub>29</sub>N<sub>7</sub>O. 1.5(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>) requires C, 58.12, H, 5.57, N, 16.95%), m/e 444 (M+1)<sup>+</sup>,  $\delta$  (360MHz, d<sub>6</sub>-DMSO) 1.90-2.06 (2H, m), 2.48-3.26 (12H, m), 3.87 (1H, s), 7.18 (1H, br s), 7.29-7.38 (7H, m), 7.49 (1H, d, J=8.6Hz), 7.62 (1H, br s), 7.79 (1H, d, J=2Hz), 9.02 (2H, s), 11.18 (1H, br s).

#### EXAMPLES 47 AND 48

(+)- and (-)-4-(1-(Phenyl)carboxamidomethyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperazine. 1.5 Hydrogen Oxalate

The racemic amide (Example 46) (121mg, 0.27mmol) was dissolved in ethanol (50mg/ml). 50 $\mu$ l of solution was injected onto a Chiralcel OD-H column (250 x 4.6mm i.d., 5 $\mu$ M) per run, using 50% ethanol in hexane as the mobile phase. Using a flow rate of 1ml/min and U.V. detection at 285nm, the two enantiomers were efficiently separated. The fractions containing each separate enantiomer were combined and evaporated *in vacuo*.

Enantiomer A (40mg): Retention time 6.5 min.  
Purity A:B = >99.5:0.5

- 85 -

Enantiomer B (41mg): Retention time 10.7min.

Purity B:A = > 99.5:0.5

5 The 1.5 hydrogen oxalate salt of each enantiomer was prepared.

Enantiomer A: mp 148-150°C, (Found: C, 58.11, H, 5.91, N, 17.04%.

C<sub>25</sub>H<sub>29</sub>N<sub>7</sub>O. 1.5(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>) requires C, 58.12, H, 5.57, N, 16.95%), m/e 444

(M+1)<sup>+</sup>, <sup>1</sup>H nmr as for Example 46.

10

Enantiomer B: mp 150-153°C, (Found: C, 58.21, H, 5.89, N, 17.01%.

C<sub>25</sub>H<sub>29</sub>N<sub>7</sub>O. 1.5(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>) requires C, 58.12, H, 5.57, N, 16.95%), m/e 444

(M+1)<sup>+</sup>, <sup>1</sup>H nmr as for Example 46.

15

#### EXAMPLE 49

4-(1-(Phenyl)-N-methylcarboxamidomethyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperazine. 1.2 Hydrogen Oxalate

20 A solution of the ester (55mg, 0.12mmol) (prepared as described in Step a) Example 46) in methanol/water (5ml (4:1)) was heated at 70°C for 5h, in the presence of potassium hydroxide (15mg, 0.27mmol). The solvent was evaporated and the residue dissolved in water. 1M HCl was added to adjust the pH to 7 then the water was  
25 removed *in vacuo*. The residue was azeotroped with toluene (2x7ml) and the crude acid used in the next reaction without further purification.

To a solution of the crude acid in anhydrous DMF (5ml) was added triethylamine (18μl, 0.13mmol), 1-hydroxybenzotriazole (19mg, 0.14mmol), methylamine (66μl of a 2.0M solution in THF, 0.13mmol) and  
30 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (25mg, 0.13mmol). The mixture was stirred at room temperature for 20h, before

removal of the solvent *in vacuo*. The residue was chromatographed on silica gel, eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (90:10:1), to afford the amide (50mg, 91%) as a colourless oil. The 1.2 hydrogen oxalate salt was prepared, mp 152°C, (Found: C, 58.55, H, 6.21, N, 16.67%. C<sub>26</sub>H<sub>31</sub>N<sub>7</sub>O.

5 1.2(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>). H<sub>2</sub>O requires C, 58.45, H, 6.11, N, 16.80%), m/e 458 (M+1)<sup>+</sup>,  $\delta$  (360MHz, d<sub>6</sub>-DMSO) 1.92-2.04 (2H, m), 2.54-3.22 (15H, m), 3.91 (1H, s), 7.30-7.42 (7H, m), 7.49 (1H, d, J=8.7Hz), 7.92 (1H, d, J=2Hz), 8.14 (1H, br q, J=4.6Hz), 9.01 (2H, s), 11.17 (1H br s).

10

#### EXAMPLE 50

4-(1-(Phenyl)-N,N-dimethylcarboxamidomethyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperazine. 1.4 Hydrogen Oxalate

15

A solution of the ester (83mg, 0.18mmol) (prepared as described in Step a) Example 46) in methanol/water (6ml (5:1)) was heated at 70°C for 20h. The solvent was evaporated and the residue dissolved in water. 1M HCl was added to adjust the pH to 7 then the water was removed *in vacuo*. The residue was azeotroped with toluene  
20 (2x10ml) and the crude acid used in the subsequent reaction without further purification.

25

To a solution of the crude acid in anhydrous DMF (5ml) was added triethylamine (27 $\mu$ l, 0.2mmol), 1-hydroxybenzotriazole (29mg, 0.22mmol), dimethylamine (40 $\mu$ l of a 5.6M solution in ethanol, 0.22mmol)  
and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (38mg, 0.2mmol). The mixture was stirred for 20h, before removal of the solvent. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (20ml) and water (20ml). The organic phase was separated, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The residue was chromatographed on silica gel, eluting with  
30 CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (90:10:1), to give the amide (67mg, 79%) as a colourless oil. The 1.4 hydrogen oxalate salt was prepared, mp 152°C,



(Found: C, 60.01, H, 6.40, N, 16.31%.  $C_{27}H_{33}N_7O \cdot 1.4(C_2H_2O_4)$  requires C, 59.89, H, 6.04, N, 16.41%), m/e 472 (M+1)<sup>+</sup>,  $\delta$  (360MHz,  $d_6$ -DMSO) 1.88-2.02 (2H, m), 2.46-3.10 (18H, m), 4.67 (1H, s), 7.26-7.42 (7H, m), 7.49 (1H, d, J=8.6Hz), 7.78 (1H, s), 9.00 (2H, s), 11.16 (1H, br s).

5

### EXAMPLE 51

4-[(2-Methylcarbamoyl-1-phenyl)ethyl]-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperazine. 1.5 Hydrogen Oxalate

10

a) 4-[(2-Amino-1-phenyl)ethyl]-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperazine

To a solution of 4-[(2-hydroxy-1-phenyl)ethyl]-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperazine [Example 52, Step a)] (0.33g, 0.77mmol) in anhydrous THF (15ml) at -10°C was added triethylamine (214 $\mu$ l, 1.53mmol) followed by methanesulphonyl chloride (118 $\mu$ l, 1.53mmol). The mixture was stirred for 15 min then the precipitate removed by filtration. The filtrate was evaporated and the residue transferred with THF (10ml) to a sealed tube. Ammonia (7.7ml of a 2.0M solution in methanol, 15.3mmol) was added and the mixture heated at 65°C for 30min. After cooling the solvents were evaporated and the residue chromatographed on silica gel, eluting with  $CH_2Cl_2$ /MeOH/ $NH_3$  (90:10:1) to give the amine (185mg, 56%) as a pale yellow foam. m/e 430 (M+1)<sup>+</sup>,  $\delta$  1.88-2.00 (2H, m), 2.38-2.76 (12H, m), 2.79 (2H, t, J=7.5Hz), 4.11 (1H, dd, J=10.4 and 3.6Hz), 7.13-7.18 (2H, m), 7.22-7.39 (5H, m), 7.47 (1H, d, J=8.6Hz), 7.59 (1H, s), 8.34 (1H, br s), 8.46 (2H, s).

25

b) 4-[(2-Methylcarbamoyl-1-phenyl)ethyl]-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperazine. 1.5 Hydrogen Oxalate

30

To a solution of the amine (60mg, 0.14mmol) in anhydrous  $CH_2Cl_2$  (5ml) at 0°C was added triethylamine (20 $\mu$ l, 0.14mmol) followed by

- 88 -

- methyl chloroformate (11 $\mu$ l, 0.14mmol). The cooling bath was removed and the mixture stirred at room temperature for 30min. The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (15ml) and washed with water (20ml). The organic phase was separated and the aqueous layer extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x20ml). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The residue was chromatographed on silica gel, eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (90:10:1), to give the title carbamate (54mg, 79%) as a colourless foam. The 1.5 hydrogen oxalate salt was prepared, mp 130°C (dec.), (Found: C, 56.92, H, 6.16, N, 15.48%. C<sub>27</sub>H<sub>33</sub>N<sub>7</sub>O<sub>2</sub> · 1.5(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>) · 0.5(H<sub>2</sub>O) requires C, 57.04, H, 5.90, N, 15.52%), m/e 488 (M+1)<sup>+</sup>,  $\delta$  (360MHz, d<sub>6</sub>-DMSO) 1.94-2.10 (2H, m), 2.42-3.20 (14H, m), 3.51 (3H, s), 4.67-4.79 (1H, m), 7.20-7.36 (7H, m), 7.50 (1H, d, J=8.6Hz), 7.78-7.86 (1H, m), 7.80 (1H, d, J=1.9Hz), 9.03 (2H, s), 11.19 (1H, br s).

15

EXAMPLE 52

4-[(2-Dimethylamino-1-phenyl)ethyl]-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperazine. 1.45 Hydrogen Oxalate

- 20 a) 4-[(2-Hydroxy-1-phenyl)ethyl]-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperazine

- To a solution of the ester (Example 46, Step a)) (620mg, 1.35mmol) in anhydrous THF (20ml) at -10°C was added LiAlH<sub>4</sub> (1.62ml of a 1.0M solution in ether, 1.62mmol) dropwise. Stirring was continued at -10°C for 2h, then sat. Na<sub>2</sub>SO<sub>4</sub> (5ml) was added and the cooling bath removed. The mixture was stirred at room temperature for 15min. then the undissolved solid filtered off. The filtrate was removed *in vacuo* and the residue chromatographed on silica gel, eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (90:10:1), to afford the alcohol (485mg, 84%) as a colourless foam. m/e 431 (M+1)<sup>+</sup>,  $\delta$  (360MHz, CDCl<sub>3</sub>) 1.81-1.90 (2H, m), 2.32-2.70 (10H, m), 2.74 (2H, t, J=7.6Hz), 3.64-3.70 (2H, m), 3.96(1H, t,

- 89 -

J=11Hz), 7.11-7.19 (4H, m), 7.28-7.35 (3H, m), 7.45 (1H, d, J=8.6Hz), 7.52 (1H, d, J=2.0Hz), 8.35 (1H, br s), 8.44 (2H, s).

5 b) 4-[(2-Dimethylamino-1-phenyl)ethyl]-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperazine. 1.45 Hydrogen Oxalate

To a solution of the alcohol (100mg, 0.23mmol) in anhydrous THF (5ml) at 0°C was added triethylamine (65µl, 0.46mmol) followed by methanesulphonyl chloride (36µl, 0.46mmol). The mixture was stirred for 45min then the undissolved solid removed by filtration. The filtrate was  
10 evaporated and the residue transferred with THF (5ml) to a sealed tube. Dimethylamine (0.83ml of a 5.6M solution in ethanol, 4.6mmol) was added and the mixture heated at 65°C for 30min. After cooling the precipitate was removed by filtration and the solvents evaporated. The residue was chromatographed on silica gel, eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (75:10:1),  
15 to give the piperazine (39mg, 37%) as a colourless foam. The 1.45 hydrogen oxalate salt was prepared, mp 150°C (dec.), (Found: C, 60.94, H, 6.87, N, 16.60%. C<sub>27</sub>H<sub>35</sub>N<sub>7</sub>. 1.45(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>) requires C, 61.06, H, 6.50, N, 16.67%), m/e 458 (M+1)<sup>+</sup>, δ (360MHz, d<sub>6</sub>-DMSO) 1.90-2.00 (2H, m), 2.36 (6H, s), 2.60-2.86 (13H, m), 3.20-3.30 (1H, m), 4.12-4.26 (1H, m), 7.30-7.33  
20 (2H, m), 7.38-7.46 (5H, m), 7.49 (1H, d, J=8.6Hz), 7.87 (1H, s), 9.02 (2H, s), 11.15 1H, br s).

EXAMPLE 53

25 4-Benzyl-1-[3-(5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propyl]piperazine oxalate

1. Intermediate 4: 5-(1,2,4-Triazol-1-yl)-1H-pyrrolo[2,3-c]pyridine

30

a) 4-Methyl-5-nitro-2-(1,2,4-triazol-1-yl)pyridine

To a solution of 1,2,4-triazole (4.0g, 58mmol) in dry DMF (20mL) was added potassium carbonate (12.0g, 87mmol) and 2-chloro-4-methyl-5-nitropyridine (10g, 58mmol) and the mixture stirred at ambient temperature under nitrogen for 24 hours. Ethyl acetate (500mL) and water (250mL) were added to the mixture and the resulting precipitate was collected by filtration to give the title compound (5.08g, 43%) as a pale brown solid. The filtrate was separated and the organic phase was washed with water (250mL) and brine (250mL), dried (MgSO<sub>4</sub>) and evaporated. The residue was triturated with ethyl acetate and the precipitate collected by filtration to give the title compound as a brown solid (4.11g, 35%, overall yield 78%). mp 198-200°C. <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 2.72 (3H, s), 7.86 (1H, s), 8.07 (1H, s), 9.03 (1H, s) and 9.15 (1H, s).

b) N,N-Dimethyl-2-(5-nitro-2-(1,2,4-triazol-1-yl)-pyridin-4-yl)ethenamine

To a suspension of 4-methyl-5-nitro-2-(1,2,4-triazol-1-yl)pyridine (4.1g, 20mmol) in dry DMF (30mL) was added dimethylformamide dimethyl acetal (5.9mL, 44mmol) and the mixture heated at 90°C for 20 min. The solvent was evaporated *in vacuo* using toluene as an azeotrope to give the title compound (5.2g, 100%) as a dark red solid. mp 225-228°C. <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 3.10 (6H, s) 6.13 (1H, d, J=13.1Hz), 7.54 (1H, d, J=13.1Hz), 7.81 (1H, s), 8.04 (1H, s), 8.92 (1H, s) and 9.17 (1H, s).

c) 5-(1,2,4-Triazol-1-yl)-1H-pyrrolo[2,3-c]pyridine

N,N-Dimethyl-2-(5-nitro-2-(1,2,4-triazol-1-yl)pyridin-4-yl)ethenamine (8g, 31mmol) was hydrogenated over platinum oxide (1.6g) in ethanol (150mL) at 30 psi of hydrogen for 1 hour. The catalyst was removed by filtration and the solvent evaporated *in vacuo*. The residue was chromatographed on silica eluting with ethyl acetate to afford an

orange/brown solid. This was triturated with ether and the precipitate collected by filtration to give the title compound (2.89g, 51%) as a pink solid. mp 203-205°C. <sup>1</sup>H NMR (360MHz, d<sub>6</sub>-DMSO) δ 6.67 (1H, d, J=3.0Hz), 7.76 (1H, d, J=2.9Hz), 8.01 (1H, s), 8.23 (1H, s), 8.70 (1H, s), 9.25 (1H, s) and 11.86 (1H, br s).

2. 3-Formyl-5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridine

A mixture of Intermediate 4 (3.86g, 20.9mmol) and hexamethylenetetramine (4.39g, 31.3mmol) was refluxed in 33% aqueous acetic acid (35mL) for 90 min. Water (40mL) was added and the mixture cooled in ice for 90 min. The precipitate was collected by filtration to give the title compound (3.31g, 74%) as a beige solid. mp 220°C (dec.). <sup>1</sup>H NMR (250MHz, d<sub>6</sub>-DMSO) δ 8.29 (1H, s), 8.46 (1H, s), 8.65 (1H, s), 8.81 (1H, s), 9.33 (1H, s), 10.04 (1H, s) and 12.78 (1H, br s).

3. 1-tert-Butyloxycarbonyl-3-formyl-5-(1,2,4-triazol-1-yl)pyrrolo[2,3-c]pyridine

To a solution of 3-formyl-5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridine (3.4g, 16mmol) in acetonitrile (75mL) was added di-tert-butyl dicarbonate (4.18g, 19mmol) and dimethylaminopyridine (98mg, 0.8mmol) and the mixture was stirred at ambient temperature under nitrogen for 16 hours. The solvent was evaporated *in vacuo* and the residue triturated with ether. The precipitate was collected by filtration and chromatographed on silica eluting with 20% EtOAc in DCM to give the title compound (3.98g, 70%) as a colourless solid. mp 190°C (dec.). <sup>1</sup>H NMR (360MHz, d<sub>6</sub>-DMSO) δ 1.70 (9H, s), 8.33 (1H, s), 8.51 (1H, s), 9.00 (1H, s), 9.20 (1H, s), 9.41 (1H, s) and 10.15 (1H, s).

4. Ethyl-3-[1-*tert*-butyloxycarbonyl-5-(1,2,4-triazol-1-yl)pyrrolo[2,3-c]pyridin-3-yl]prop-2-enoate

A solution of 1-*tert*-butyloxycarbonyl-3-formyl-5-(1,2,4-triazol-1-yl)pyrrolo[2,3-c]pyridine (1.5g, 4.8mmol) and  
5 (carboethoxymethylene)triphenylphosphorane (2.0g, 5.8mmol) in toluene (30mL) was heated at 80°C under nitrogen for 90 min. The mixture was allowed to cool and the solvent was evaporated *in vacuo*. The residue was chromatographed on silica eluting with 20% EtOAc in DCM to give a colourless solid. This was triturated with ether and the solid  
10 rechromatographed on silica with 20% EtOAc in DCM to give the title compound (1.77g, 96%) as a colourless solid. mp 178-181°C. <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.37 (3H, t, J=7.1Hz), 1.73 (9H, s), 4.31 (2H, q, J=7.1Hz), 6.59 (1H, d, J=16.2Hz), 7.81 (1H, d, J=16.2Hz), 8.03 (1H, s), 8.14 (1H, s), 8.30 (1H, s), 9.21 (1H, s) and 9.26 (1H, br s).

15

5. Ethyl-3-(5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)prop-2-enoate

A solution of ethyl-3-[1-*tert*-butyloxycarbonyl-5-(1,2,4-triazol-1-yl)pyrrolo[2,3-c]pyridin-3-yl]prop-2-enoate (1.73g, 4.5mmol) and  
20 trifluoroacetic acid (5mL) in dry DCM (20mL) was stirred at ambient temperature under nitrogen for 5 hours. The solvent was evaporated *in vacuo* and the residue azeotroped with toluene. The residue was chromatographed on silica eluting with 20% EtOAc in DCM followed by a gradient of 5 to 10% MeOH in DCM to give a colourless solid. This was  
25 triturated with ether to give the title compound (1.05g, 82%) as a colourless solid. mp 235-238°C. <sup>1</sup>H NMR (360MHz, d<sub>6</sub>-DMSO) δ 1.29 (3H, t, J=7.1Hz), 4.20 (2H, q, J=7.1Hz), 6.44 (1H, d, J=16.0Hz), 7.92 (1H, d, J=16.1Hz), 8.22 (1H, s), 8.27 (1H, s), 8.33 (1H, d, J=2.7Hz), 8.76 (1H, s), 9.31 (1H, s) and 12.46 (1H, br s).

30

6. Ethyl 3-(5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propionate

Ethyl-3-(5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)prop-2-enoate (0.5g, 1.8mmol) was hydrogenated over palladium on carbon (10%, 0.2g) in methanol (75mL) at 45 psi of hydrogen for 90 min.

- 5 The catalyst was removed by filtration and the solvent evaporated *in vacuo* to give the title compound (0.455g, 90%) as a colourless solid. mp 129-131°C. <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.24 (3H, t, J=7.1Hz), 2.72 (2H, t, J=7.4Hz), 3.13 (2H, t, J=7.4Hz), 4.14 (2H, q, J=7.1Hz), 7.31 (1H, d, J=2.3Hz), 8.08 (1H, s), 8.11 (1H, s), 8.54-8.60 (2H, m) and 9.15 (1H, s).

10

7. 3-(5-(1,2,4-Triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propanoic acid (4-benzylpiperazinyl)amide

- To a solution of ethyl 3-(5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propionate (0.43g, 1.5mmol) in methanol (20mL) was added NaOH (4M, 1mL) and the mixture was heated at 50°C for 5 hours. After cooling the solution was neutralised (5M, HCl) and the solvents evaporated *in vacuo* to give 3-(5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propionic acid (0.65g) as a colourless solid. <sup>1</sup>H NMR (360MHz, d<sub>6</sub>-DMSO) δ 2.60 (2H, t, J=7.5Hz), 2.98 (2H, t, J=7.4Hz), 7.55 (1H, s), 7.98 (1H, s), 8.23 (1H, s), 8.62 (1H, s), 9.24 (1H, s) and 11.74 (1H, br s). This was used without purification in the next step.
- 15
- 20

- To a suspension of 3-(5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propionic acid (0.65g) in dry DMF (5mL) was added 1-benzylpiperazine (0.36mL, 2.3mmol), 1-hydroxybenzotriazole (0.255g, 1.9mmol), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (0.362g, 1.9mmol) and triethylamine (0.26mL, 1.9mmol) and this mixture was stirred at ambient temperature under nitrogen for 16 hours. The solvent was evaporated *in vacuo* and the residue was partitioned between ethyl acetate (25mL) and water (25mL) and Na<sub>2</sub>CO<sub>3</sub> (sat., 1mL). The two phases were separated and the aqueous phase was extracted with ethyl acetate (3x25mL). The combined organics were dried (Na<sub>2</sub>SO<sub>4</sub>) and
- 25
- 30

evaporated *in vacuo*. The residue was chromatographed on silica eluting with a gradient of 5 to 10% MeOH in DCM to give the title compound (0.625g, 100%) as a pale yellow foam. <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 2.28-2.46 (4H, m), 2.70 (2H, t, J=7.1Hz), 3.15 (2H, t, J=7.2Hz), 3.37-3.43 (2H, m), 3.50 (2H, s), 3.60-3.68 (2H, m), 7.23-7.34 (6H, m), 8.05 (1H, s), 8.10 (1H, s), 8.58 (1H, s), 8.69 (1H, br s) and 9.14 (1H, s).

8. 4-Benzyl-1-[3-(5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propyl]piperazine oxalate

10 To a solution of LiAlH<sub>4</sub> in ether (1.0M, 2.2mL, 2.2mmol) and dry THF (5mL) was added dropwise a solution of 3-(5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propionic acid (4-benzylpiperazinyl)amide (0.3g, 0.72mmol) in dry THF (5mL) at ambient temperature. The mixture was heated at 50°C for 30 min. After cooling water (87μL) was added  
15 followed by sodium hydroxide (4M, 87μL), followed by water (260μL). The solid was removed by filtration and the solvent evaporated *in vacuo*. The residue was chromatographed on silica eluting with a gradient of 5 to 10% MeOH in DCM followed by 90:10:1, DCM:MeOH:NH<sub>3</sub> to give the free base (0.188g, 65%) as a pale yellow foam. The free base was dissolved in  
20 Et<sub>2</sub>O:MeOH (10:1, 5mL) and treated dropwise with a solution of oxalic acid (42mg, 0.47mmol) in ether (1mL). The precipitate formed was collected by filtration to give the title compound (170mg) as a cream solid. mp 180°C (dec.). Found: C, 58.01; H, 5.79; N, 18.20. C<sub>23</sub>H<sub>27</sub>N<sub>7</sub>·1.5(CO<sub>2</sub>H)<sub>2</sub> requires C, 58.20; H, 5.64; N, 18.27%. <sup>1</sup>H NMR (360MHz, d<sub>6</sub>-DMSO) δ  
25 1.92 (2H, m), 2.53-3.24 (12H, m), 3.64 (2H, d), 7.27-7.40 (5H, m), 7.60 (1H, s), 7.99 (1H, s), 8.23 (1H, s), 8.65 (1H, s), 9.25 (1H, s) and 11.70 (1H, br s).



EXAMPLE 544-Benzyl-1-[3-(5-(1,2,4-triazol-4-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propyl]piperazine oxalate

5

1. Intermediate 5: 5-(1,2,4-Triazol-4-yl)-1H-pyrrolo[2,3-c]pyridinea) 2-Acetyl-amino-4-methyl-5-nitropyridine

2-Amino-4-methyl-5-nitropyridine (28.4g, 0.185mol) was  
10 heated at 90°C in acetic anhydride (100mL) for 3 hours. After cooling the  
solvent was evaporated *in vacuo* and the residue was azeotroped with  
toluene to give a yellow solid. This was triturated with ether and the solid  
was collected by filtration to give the title compound (33.8g, 93%) as a pale  
yellow solid. mp 153-154°C. <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 2.27 (3H, s),  
15 2.70 (3H, s), 8.17 (1H, br s), 8.24 (1H, s) and 8.96 (1H, s).

b) N,N-Dimethyl-2-(2-acetyl-amino-5-nitropyridin-4-yl)ethenamine

To a solution of 2-acetyl-amino-4-methyl-5-nitropyridine  
(33.8g, 0.173 mol) in dry DMF (300mL) was added dimethylformamide  
20 dimethyl acetal (50.7mL, 0.381mol) and the mixture heated at 90°C for 90  
min. The solvent was evaporated *in vacuo* using toluene as an azeotrope.  
The residue was triturated with ether and the solid collected by filtration  
to give the title compound (33g, 76%) as an orange solid. mp 193-196°C.  
<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ 2.23 (3H, s), 3.04 (6H, s), 6.12 (1H, d,  
25 J=13.1Hz), 7.43 (1H, d, J=13.1Hz), 8.17 (1H, br s), 8.27 (1H, s) and 8.83  
(1H, s).

c) 5-Acetyl-amino-1H-pyrrolo[2,3-c]pyridine

N,N-Dimethyl-2-(2-acetyl-amino-5-nitropyridin-4-  
30 yl)ethenamine (6g, 24mmol) was hydrogenated over platinum oxide (0.5g)  
in ethanol (120mL) at 35psi of hydrogen for 15 min. The catalyst was

removed by filtration and the solvent evaporated *in vacuo*. The residue was chromatographed on silica eluting with a gradient of 5 to 10% MeOH in DCM to afford a purple solid. This was triturated with ether and the precipitate collected by filtration to give the title compound (1.4g, 33%) as a beige solid. mp 220°C (dec.). <sup>1</sup>H NMR (360MHz, d<sub>6</sub>-DMSO) δ 2.07 (3H, s), 6.45 (1H, s), 7.55-7.57 (1H, m), 8.21 (1H, s), 8.46 (1H, s), 10.16 (1H, br s) and 11.42 (1H, br s).

d) 5-Amino-1H-pyrrolo[2,3-c]pyridine

5-Acetylamino-1H-pyrrolo[2,3-c]pyridine (0.61g, 3.5mmol) was heated at reflux in methanolic KOH (2M, 15mL) under nitrogen for 8 hours. The solvent was evaporated *in vacuo* and the residue partitioned between dichloromethane (100mL) and water (100mL). The two layers were separated and the aqueous phase was extracted with n-butanol (3x100mL). The combined organics were evaporated *in vacuo* and the residue chromatographed on silica eluting with 5 to 10% MeOH in DCM followed by a gradient of 90:10:1 to 80:20:1, DCM:MeOH:NH<sub>3</sub> to give the title compound (0.384g, 83%) as a red solid. mp 183-186°C. <sup>1</sup>H NMR (360MHz, d<sub>6</sub>-DMSO) δ 4.95 (2H, br s), 6.13-6.15 (1H, m), 6.52 (1H, s), 7.34-7.37 (1H, m), 8.17 (1H, s) and 10.90 (1H, br s).

e) 5-(1,2,4-Triazol-4-yl)-1H-pyrrolo[2,3-c]pyridine

5-Amino-1H-pyrrolo[2,3-c]pyridine (2g, 15mmol), diformylhydrazine (1.32g, 15mmol) and dry DMF (1.5mL) were heated at 170°C under nitrogen for 4 hours. After cooling, ethyl acetate (10mL) and water (10mL) were added. The mixture was stirred vigorously for 15 min. The resulting precipitate was collected by filtration, and chromatographed on silica eluting with a gradient of 5 to 7 to 10% MeOH in DCM to give a yellow solid. This was triturated with ether to give the title compound (1.65g, 59%) as a yellow/green crystalline solid. mp 254-257°C. <sup>1</sup>H NMR

- 97 -

(360MHz,  $d_6$ -DMSO)  $\delta$  6.63 (1H, d,  $J=3.1$ Hz), 7.79 (1H, d,  $J=3.0$ Hz), 7.99 (1H, s), 8.71 (1H, s), 9.21 (2H, s) and 11.89 (1H, br s).

2. 3-Formyl-5-(1,2,4-triazol-4-yl)-1H-pyrrolo[2,3-c]pyridine

5                   A mixture of Intermediate 5 (1.62g, 8.7mmol) and hexamethylenetetramine (1.47g, 10.5mmol) was refluxed in 33% aqueous acetic acid (10mL) for 75 min. The mixture was cooled in ice for 2 hours and the precipitate was collected by filtration to give the title compound (0.71g, 38%) as a beige solid. The filtrate was evaporated and the residue  
10 chromatographed on silica eluting with 10% MeOH in DCM to give the title compound (0.39g, 21%) (overall yield 59%), as a yellow solid. mp 155°C (dec.).  $^1\text{H}$  NMR (360MHz,  $d_6$ -DMSO)  $\delta$  8.35 (1H, s), 8.68 (1H, s), 8.83 (1H, s), 9.30 (2H, s), 10.05 (1H, s) and 12.74 (1H, br s).

15   3. 1-tert-Butyloxycarbonyl-3-formyl-5-(1,2,4-triazol-4-yl)pyrrolo[2,3-c]pyridine

                  To a solution of 3-formyl-5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridine (1.1g, 5.2mmol) in acetonitrile (30mL) was added di-tert-butylidicarbonate (1.69g, 7.8mmol) and dimethylaminopyridine (63mg, 0.52mmol) and the mixture was stirred at ambient temperature under  
20 nitrogen for 16 hours. The solvent was evaporated *in vacuo* and the residue chromatographed on silica eluting with a gradient of 2 to 5% MeOH in DCM to give a yellow solid. This was triturated with ether. The precipitate was collected by filtration to afford the title compound (0.71g,  
25 49%) as a cream solid. mp 170°C (dec.).  $^1\text{H}$  NMR (360MHz,  $d_4$ -MeOH)  $\delta$  1.76 (9H, s), 8.49 (1H, s), 8.80 (1H, s), 9.29 (2H, s), 9.34 (1H, s) and 10.12 (1H, s).

4. Ethyl 3-[5-(1,2,4-triazol-4-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl]prop-2-enoate

A solution of 1-*tert*-butyloxycarbonyl-3-formyl-5-(1,2,4-triazol-4-yl)pyrrolo[2,3-c]pyridine (0.71g, 2.3mmol) and (carboethoxymethylene)triphenylphosphorane (0.95g, 2.7mmol) in toluene (25mL) was heated at 80°C under nitrogen for 2 hours. The mixture was allowed to cool and the solvent evaporated *in vacuo*. The residue was chromatographed on silica eluting with 20% EtOAc in DCM, followed by a gradient of 2 to 5% MeOH in DCM to afford ethyl 3-[1-*tert*-butyloxycarbonyl-5-(1,2,4-triazol-4-yl)pyrrolo[2,3-c]pyridin-3-yl]prop-2-enoate (0.93g), contaminated with minor impurities, as a cream solid. <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.38 (3H, t, J=7.1Hz), 1.73 (9H, s), 4.32 (2H, q, J=7.1Hz), 6.51 (1H, d, J=16.2Hz), 7.76 (1H, s), 7.80 (1H, d, J=15.7Hz), 8.09 (1H, s), 8.95 (2H, s) and 9.33 (1H, s). This was used without further purification.

A solution of ethyl 3-[1-*tert*-butyloxycarbonyl-5-(1,2,4-triazol-4-yl)pyrrolo[2,3-c]pyridin-3-yl]prop-2-enoate (0.92g) and trifluoroacetic acid (5mL) in dry DCM (20mL) was stirred at ambient temperature under nitrogen for 16 hours. The solvent was evaporated *in vacuo* and the residue azeotroped with toluene. The residue was chromatographed on silica eluting with 5 to 20% MeOH in DCM to give a cream solid. This was triturated with MeOH and the solid was collected by filtration to afford the title compound (0.4g, 62%) as a cream solid. mp 235°C (dec.). <sup>1</sup>H NMR (360MHz, d<sub>6</sub>-DMSO) δ 1.29 (3H, t, J=7.1Hz), 4.21 (2H, q, J=7.1Hz), 6.68 (1H, d, J=16.2Hz), 7.91 (1H, d, J=16.1Hz), 8.33 (1H, s), 8.36 (1H, s), 8.74 (1H, s), 9.35 (2H, s) and 12.44 (1H, br s).

5. Ethyl 3-(5-(1,2,4-triazol-4-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propionate

Ethyl 3-(5-(1,2,4-triazol-4-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)prop-2-enoate (0.4g, 1.4mmol) was hydrogenated over palladium on carbon (10%, 0.25g) in ethanol (50mL) at 45psi of hydrogen for 6 hours.

The catalyst was removed by filtration and the solvent evaporated *in vacuo* to give the title compound (0.32g, 80%) as a colourless solid. mp 215-218°C. <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>: d<sub>4</sub>-MeOH 9:1) δ 1.23 (3H, t, J=7.1Hz), 2.72 (2H, t, J=7.4Hz), 3.12 (2H, t, J=7.4Hz), 4.13 (2H, q, J=7.1Hz), 7.36 (1H, s), 7.61 (1H, s), 8.60 (1H, s) and 8.89 (2H, s).

6. 3-(5-(1,2,4-Triazol-4-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propionic acid (4-benzylpiperazinyl)amide

To a solution of ethyl 3-(5-(1,2,4-triazol-4-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propionate (0.115g, 0.4mmol) in methanol (5mL) was added NaOH (4M, 0.5mL, 2mmol) and the mixture heated at 40°C for 16 hours. After cooling the solution was neutralised (5M HCl) and the solvents evaporated to give 3-(5-(1,2,4-triazol-4-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propionic acid (0.23g) as a colourless solid. <sup>1</sup>H NMR (360MHz, d<sub>6</sub>-DMSO) δ 2.48-2.55 (2H, m), 2.96 (2H, t, J=7.1Hz), 7.54 (1H, s), 8.03 (1H, s), 8.62 (1H, s), 9.24 (2H, s) and 11.81 (1H, br s). This was used without further purification in the next step.

To a suspension of 3-(5-(1,2,4-triazol-4-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propionic acid (0.23g) in dry DMF (3mL) was added 1-benzylpiperazine (0.1mL, 0.58mmol), 1-hydroxybenzotriazole (66mg, 0.49mmol), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (93mg, 0.49mmol) and triethylamine (68μL, 0.4mmol) and this mixture was stirred at ambient temperature under nitrogen for 24 hours. The solvent was evaporated *in vacuo* and the residue partitioned between ethyl acetate (25mL) and water (20mL). The two phases were separated and the aqueous phase was extracted with ethyl acetate (3x25mL). The combined organics were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated *in vacuo*. The residue was chromatographed on silica eluting with 90:10:1, DCM:MeOH:NH<sub>3</sub> to give the title compound (30mg, 19%) as a colourless solid. mp 185°C (dec.). <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>:d<sub>4</sub>-MeOH 9:1) δ 2.29-2.34 (2H, m), 2.35-2.42 (2H, m), 2.70 (2H, t, J=7.4Hz), 3.12 (2H, t,

J=7.4Hz), 3.36-3.43 (2H, m), 3.48 (2H, s), 3.58-3.64 (2H, m), 7.24-7.35 (5H, m), 7.37 (1H, s), 7.67 (1H, s), 8.60 (1H, s) and 8.93 (2H, s).

7. 4-Benzyl-1-[3-(5-(1,2,4-triazol-4-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propyl]piperazine oxalate

To a suspension of 3-(5-(1,2,4-triazol-4-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propionic acid (4-benzylpiperazinyl)amide (30mg, 0.073mmol) in dry THF (3mL) was added dropwise a solution of LiAlH<sub>4</sub> in ether (1.0M, 144μL, 0.144mmol). The mixture was stirred at ambient temperature under nitrogen for 5 min and then heated at 50°C for another 10 min. Further LiAlH<sub>4</sub> in ether (1M, 73μL, 0.073mmol) was added and the mixture heated at 50°C for another 10 min. After cooling, water (9μL) was added followed by sodium hydroxide (4M, 9μL), followed by water (27μL). The solid was removed by filtration and the solvent evaporated *in vacuo*. The residue was chromatographed on silica eluting with 90:10:1, DCM:MeOH:NH<sub>3</sub> to give the free base (20mg, 69%) as a colourless solid. The free base (15mg, 0.037mmol) was dissolved in ether:MeOH (2:3, 5mL) and treated dropwise with a solution of oxalic acid (3.4mg, 0.037mmol) in ether (1mL). The precipitate formed was collected by filtration to give the title compound (12mg) as a cream solid. mp 148°C (dec.). Found: C, 56.00; H, 5.76; N, 16.20. C<sub>23</sub>H<sub>27</sub>N<sub>7</sub>·2.05(CO<sub>2</sub>H)<sub>2</sub>·0.1(Et<sub>2</sub>O) requires C, 55.65; H, 5.45; N, 16.52%. <sup>1</sup>H NMR (360MHz, d<sub>6</sub>-DMSO) δ 1.94-2.06 (2H, m), 2.46-3.16 (12H, m), 3.62 (2H, s), 7.23-7.38 (5H, m), 7.59 (1H, s), 7.99 (1H, s), 8.64 (1H, s), 9.21 (2H, s) and 11.67 (1H, br s).

25

30

EXAMPLE 55

4-[2-(4-Acetamidophenyl)ethyl]-1-[3-(5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propyl]piperazine. 1.65 Hydrogen Oxalate

5

a) 3-(5-(1,2,4-Triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propionic acid (4-tert-butyloxycarbonylpiperazinyl)amide

To a solution of 3-(5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl) propionic acid (0.34g, 1.3mmol) (prepared as described in  
10 Example 53 Step 7) in anhydrous DMF (5ml) was added 1-tert-butyloxycarbonylpiperazine (0.5g, 2.7mmol), 1-hydroxybenzotriazole (225mg, 1.7mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.45g, 2.3mmol) and triethylamine (0.23ml, 1.7mmol). The mixture was stirred at room temperature for 2 days. The solvent was  
15 evaporated and the residue partitioned between ethyl acetate (25ml) and water (20ml). The organic layer was separated and the aqueous phase extracted with ethyl acetate (3x20ml). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The residue was chromatographed on silica gel, eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH (90:10) to afford the title compound,  
20 with some impurities, as a pale yellow foam.

The process was repeated using the acid (78mg, 0.3mmol), 1-(tert-butyloxycarbonyl)piperazine (113mg, 0.61mmol), 1-hydroxybenzotriazole (51mg, 0.38mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (101mg, 0.53mmol) and triethylamine  
25 (74μl, 0.53mmol). The residue was combined with the pale yellow foam from the first run and chromatographed on silica gel, eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH (90:10). The desired amide (478mg, 70%) was isolated as a colourless foam, m/e 426 (M+1)<sup>+</sup>, δ (360MHz, CDCl<sub>3</sub>) 1.46 (9H, s), 2.72 (2H, t, J=7.2Hz), 3.17 (2H, t, J=7.2Hz), 3.30-3.42 (6H, m), 3.60-3.64 (2H, m),  
30 7.35 (1H, s), 8.06 (1H, s), 8.10 (1H, s), 8.56 (1H, s), 8.66 (1H, br s), 9.15 (1H, s).

b) 4-(tert-Butyloxycarbonyl)-1-[3-(5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propyl]piperazine

To a solution of the amide (0.21g, 0.49mmol) in anhydrous  
5 THF (10ml) was added LiAlH<sub>4</sub> (1.48ml of a 1.0M solution in ether,  
1.48mmol) dropwise. The mixture was stirred at room temperature for  
10min before the sequential addition of water (59μl), sodium hydroxide  
(4M, 59μl) and water (175μl). The resultant solid was removed by  
filtration and the filtrate evaporated. The residue was chromatographed  
10 on silica gel, eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (90:10:1), to give the title  
amine (125mg, 62%) as a pale yellow gum, m/e 412 (M+1)<sup>+</sup>, δ (250MHz, d<sub>4</sub>-  
MeOH) 1.45 (9H, s), 1.88-2.00 (2H, m), 2.39-2.47 (6H, m), 2.85 (2H, t,  
J=7.4Hz), 3.41-3.45 (4H, m), 7.46 (1H, s), 8.07 (1H, s), 8.16 (1H, s), 8.60  
(1H, s), 9.21 (1H, s).

15

c) 4(H)-1-[3-(5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propyl]piperazine

To a solution of the carbamate (128mg, 0.31mmol) in  
anhydrous dichloromethane (20ml) was added trifluoroacetic acid (2ml).  
20 The mixture was stirred at room temperature for 3h then the solvent was  
evaporated and the residue azeotroped with toluene (2x20ml). The  
residue was partitioned between nBuOH (4x25ml) and NaOH (1M, 25ml).  
The combined organic layers were evaporated and the residue  
chromatographed on silica, eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (40:10:1) to  
25 give the deprotected amine (80mg, 83%) as a pale yellow gum, m/e 312  
(M+1)<sup>+</sup>, δ (250MHz, d<sub>4</sub>-MeOH) 1.80-1.91 (2H, m), 2.32-2.46 (6H, m), 2.75  
(2H, t, J=7.3Hz), 2.82-2.86 (4H, m), 7.37 (1H, s), 7.97 (1H, s), 8.07 (1H, s),  
8.49 (1H, s), 9.12 (1H, s).

30



d) 4-[2-(4-Acetamidophenyl)ethyl]-1-[3-(5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propyl]piperazine. 1.65 Hydrogen Oxalate

To a solution of the amine (86mg, 0.26mmol) in anhydrous DMF (3ml) was added K<sub>2</sub>CO<sub>3</sub> (71mg, 0.51mmol) and 2-(4-acetamidophenyl)ethyl bromide (75mg, 0.31mmol). The mixture was partitioned between dichloromethane (20ml) and water (20ml). The aqueous phase was extracted with dichloromethane (20ml) followed by butanol (20ml). The combined organics were evaporated and the residue chromatographed on silica, eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (40:10:1) to give the title compound (75mg, 62%) as a colourless solid. The 1.65 hydrogen oxalate salt was prepared, mp 190°C(dec.), (Found: C, 55.08, H, 5.93, N, 17.58%. C<sub>26</sub>H<sub>32</sub>N<sub>8</sub>O. 1.65(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>). H<sub>2</sub>O requires C, 55.06, H, 5.88, N, 17.53%), m/e 473 (M+1)<sup>+</sup>, δ (360MHz, d<sub>6</sub>-DMSO) 1.88-2.02 (5H, m), 2.66-3.14 (16H, m), 7.15 (2H, d, J=8.4Hz), 7.48 (2H, d, J=8.4Hz), 7.59 (1H, s), 7.99 (1H, s), 8.23 (1H, s), 8.64 (1H, s), 9.25 (1H, s), 9.87 (1H, s), 11.68 (1H, br s).

**EXAMPLE 56**

20 4-[2-(4-Acetamidophenyl)ethyl]-1-[3-(5-(1,2,4-triazol-4-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propyl]piperazine. 2 Hydrogen Oxalate

a) 4(H)-1-[3-(5-(1,2,4-triazol-4-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propyl]piperazine

25 A solution of 4-benzyl-1-[3-(5-(1,2,4-triazol-4-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propyl]piperazine (Example 54) (59mg, 0.15mmol) in ethanol (25ml) was hydrogenated at 45 psi for 4h in the presence of palladium hydroxide on carbon (Pearlman's catalyst) (175mg). The catalyst was removed by filtration and the solvent evaporated. The residue was chromatographed on silica, eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (40:10:1) to give the piperazine (38mg, 79%) as a pale yellow gum. m/e

312 (M+1)<sup>+</sup>,  $\delta$  (250MHz, CDCl<sub>3</sub> + d<sub>4</sub>-MeOH) 1.91-1.98 (2H, m), 2.56 (2H, t, J=5.3Hz), 2.70-2.78 (4H, m), 2.83 (2H, t, J=5.3Hz), 3.14-3.24 (4H, m), 7.39 (1H, s), 7.67 (1H, s), 8.62 (1H, s), 8.97 (2H, s).

5    b) 4-[2-(4-Acetamidophenyl)ethyl]-1-[3-(5-(1,2,4-triazol-4-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propyl]piperazine. 2 Hydrogen Oxalate

To a solution of the piperazine prepared in Step a) (52mg, 0.17mmol) in anhydrous DMF (2ml) was added K<sub>2</sub>CO<sub>3</sub> (46mg, 0.33mmol) and 2-(4-acetamidophenyl)ethyl bromide (49mg, 0.2mmol). The mixture  
10    was heated at 50°C for 5h then the solvent was evaporated. The residue was chromatographed on silica, eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (90:10:1→40:10:1) to give the title compound (37mg, 46%) as a colourless solid. The 2.0 hydrogen oxalate salt was prepared, mp 138°C (dec.), (Found: C, 52.31, H, 6.06, N, 16.63%. C<sub>26</sub>H<sub>32</sub>N<sub>8</sub>O. 2(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>). 2(H<sub>2</sub>O)  
15    requires C, 52.32, H, 5.85, N, 16.27%), m/e 473 (M+1)<sup>+</sup>,  $\delta$  (360MHz, d<sub>6</sub>-DMSO) 1.90-2.01 (5H, m), 2.66-3.10 (16H, m), 7.14 (2H, d, J=8.4Hz), 7.48 (2H, d, J=8.4Hz), 7.60 (1H, s), 8.00 (1H, s), 8.64 (1H, s), 9.22 (2H, s), 9.87 (1H, s), 11.68 (1H, br s).

20

EXAMPLE 57

1-(3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl)-4-(4-fluorophenyl)methylpiperazine. 2.5 Hydrogen Oxalate

25

Prepared from Intermediate 2 and 4-fluorobenzaldehyde using the general reductive amination procedure; mp. 213-215°C; (Found: C, 53.91, H, 5.22, N, 12.73. C<sub>24</sub>H<sub>27</sub>N<sub>6</sub>F. 2.5(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>) requires C, 54.12, H, 5.01, N, 13.05%),  $\delta$  (250MHz, d<sub>6</sub>-DMSO) 1.92-2.08 (2H, m, CH<sub>2</sub>), 2.52-3.22 (14H, m, 7 of CH<sub>2</sub>), 3.59 (2H, s, CH<sub>2</sub>), 7.10-7.40 (6H, m, Ar-H), 7.49 (1H, d, J=8.6Hz, Ar-H), 7.80 (1H, d, J=1.9Hz, Ar-H), 9.03 (2H, s, Ar-H), 11.21  
30    (1H, s, NH).

EXAMPLE 58

5 4-([N-Methyl-2-methylcarbamoyl-1-phenyl]ethyl)-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine. 1.3 Hydrogen Oxalate.

a) 4-([2-N-Methylamino-1-phenyl]ethyl)-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine

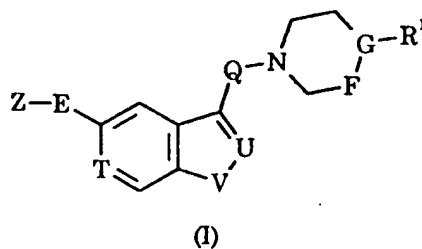
The title compound was prepared in the same manner as that  
10 described in Example 51 Step a), replacing ammonia with methylamine.  $\delta$  (250MHz, CDCl<sub>3</sub>) 1.86-1.98 (2H, m), 2.89 (3H, s), 2.33-2.82 (14H, m), 3.60 (1H, dd, J=10.9 and 3.4Hz), 7.12-7.16 (2H, m), 7.24-7.34 (5H, m), 7.48 (1H, d, J=8.5Hz), 7.56 (1H, d, J=2.0Hz), 8.47 (2H, s), 8.70 (1H, br s).

15 b) 4-([N-Methyl-2-methylcarbamoyl-1-phenyl]ethyl)-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine. 1.3 Hydrogen Oxalate

The title compound was prepared in the same manner as that  
described in Example 51, Step b, using the piperazine prepared above. mp  
160°C, (Found: C, 57.82, H, 6.38, N, 15.34%. C<sub>28</sub>H<sub>35</sub>N<sub>7</sub>O<sub>2</sub>. 1.3(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>). H<sub>2</sub>O  
20 requires C, 57.73, H, 6.27, N, 15.40%), m/e 502 (M+1)<sup>+</sup>,  $\delta$  (360MHz, d<sub>6</sub>-DMSO) 1.99-2.10 (2H, m), 2.61 (3H, s), 2.72-3.10 (14H, m), 3.63 (3H, s), 5.37-5.50 (1H, m), 7.26-7.42 (7H, m), 7.51 (1H, d, J=8.6Hz), 7.81 (1H, s), 9.02 (2H, s), 11.18 (1H, br s).

**CLAIMS:**

1. A subtype-selective 5-HT<sub>1D</sub> receptor agonist having a human 5-HT<sub>1D $\alpha$</sub>  receptor binding affinity (IC<sub>50</sub>) below 50 nM and at least a  
5 10-fold selective affinity for the 5-HT<sub>1D $\alpha$</sub>  receptor subtype relative to the 5-HT<sub>1D $\beta$</sub>  subtype.
2. A subtype-selective 5-HT<sub>1D</sub> receptor agonist having a human 5-HT<sub>1D $\alpha$</sub>  receptor binding affinity (IC<sub>50</sub>) below 10 nM and at least a  
10 50-fold selective affinity for the 5-HT<sub>1D $\alpha$</sub>  receptor subtype relative to the 5-HT<sub>1D $\beta$</sub>  subtype.
3. A compound of formula I, or a salt or prodrug thereof:



15

wherein

- Z represents an optionally substituted five-membered heteroaromatic ring selected from furan, thiophene, pyrrole, oxazole,  
20 thiazole, isoxazole, isothiazole, imidazole, pyrazole, oxadiazole, thiadiazole, triazole and tetrazole;

E represents a chemical bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;

- Q represents a straight or branched alkylene chain  
25 containing from 1 to 6 carbon atoms, optionally substituted in any position by a hydroxy group;

T represents nitrogen or CH;

U represents nitrogen or C-R<sup>2</sup>;

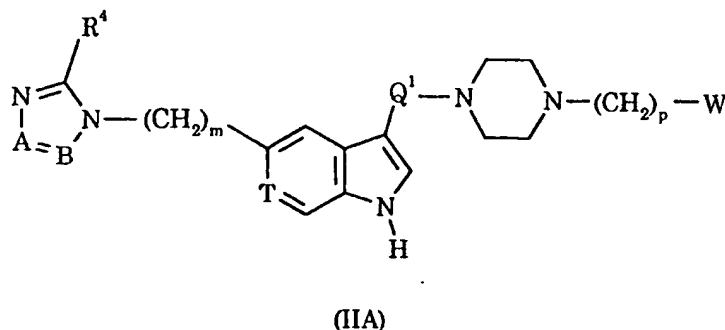
V represents oxygen, sulphur or N-R<sup>3</sup>;

-F-G- represents -CH<sub>2</sub>-N-, -CH<sub>2</sub>-CH- or -CH=C-;

R<sup>1</sup> represents C<sub>3-6</sub> alkenyl, C<sub>3-6</sub> alkynyl, aryl(C<sub>1-6</sub>)alkyl or  
 5 heteroaryl(C<sub>1-6</sub>)alkyl, any of which groups may be optionally substituted;  
 and

R<sup>2</sup> and R<sup>3</sup> independently represent hydrogen or C<sub>1-6</sub> alkyl.

4. A compound as claimed in claim 3 represented by  
 10 formula IIA, and salts and prodrugs thereof:



wherein

15 m is zero, 1, 2 or 3;

p is 1, 2 or 3;

Q¹ represents a straight or branched alkylene chain  
 containing from 2 to 5 carbon atoms, optionally substituted in any position  
 by a hydroxy group;

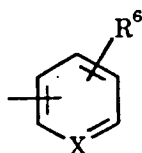
20 T represents nitrogen or CH;

A represents nitrogen or CH;

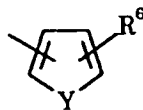
B represents nitrogen or C-R<sup>5</sup>;

R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen, C<sub>1-6</sub> alkyl, C<sub>2-6</sub>  
 alkenyl, C<sub>3-7</sub> cycloalkyl, aryl, aryl(C<sub>1-6</sub>)alkyl, C<sub>3-7</sub> heterocycloalkyl,  
 25 heteroaryl, heteroaryl(C<sub>1-6</sub>)alkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylthio, amino, C<sub>1-6</sub>  
 alkylamino, di(C<sub>1-6</sub>)alkylamino, halogen, cyano or trifluoromethyl; and

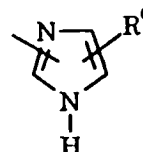
W represents a group of formula (a), (b) or (c):



(a)



(b)



(c)

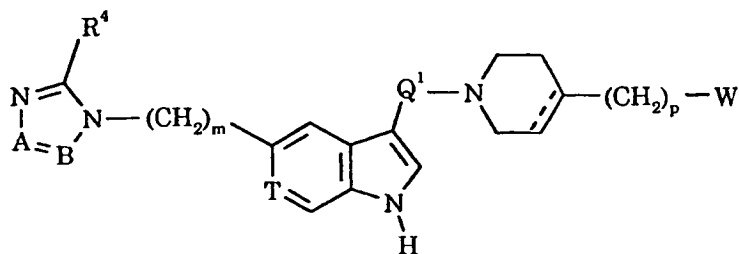
5 in which

X represents CH or nitrogen;

Y represents oxygen, sulphur or NH; and

R<sup>6</sup> represents hydrogen, halogen, cyano, trifluoromethyl, triazolyl, tetrazolyl, C<sub>1-6</sub> alkyl-tetrazolyl, C<sub>1-6</sub> alkoxy, C<sub>2-6</sub> alkylcarbonyl, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylaminomethyl, C<sub>2-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkylsulphonylamino, aminocarbonylamino, C<sub>1-6</sub> alkylaminocarbonyl, aminosulphonyl or C<sub>1-6</sub> alkylaminosulphonylmethyl.

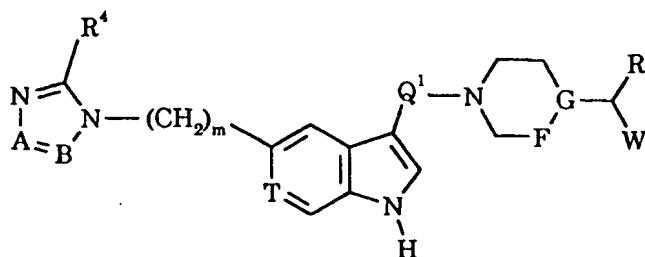
5. A compound as claimed in claim 3 represented by  
15 formula IIB, and salts and prodrugs thereof:



(IIB)

wherein the broken line represents an optional chemical bond; and  
20 m, p, Q<sup>1</sup>, T, A, B, R<sup>4</sup> and W are as defined in claim 4.

6. A compound as claimed in claim 3 represented by  
formula IIC, and salts and prodrugs thereof:



(IIC)

wherein

- 5                   T, F and G are as defined in claim 1;  
                   m, Q<sup>1</sup>, R<sup>4</sup>, A, B and W are as defined in claim 4; and  
                   R<sup>7</sup> represents hydrogen, aminomethyl, C<sub>1-6</sub>  
                   alkylaminomethyl, di(C<sub>1-6</sub>)alkylaminomethyl, C<sub>2-6</sub>  
                   alkoxycarbonylaminomethyl, [N-(C<sub>1-6</sub>)alkyl-N-  
 10               (C<sub>2-6</sub>)alkoxycarbonyl]aminomethyl, aminocarbonyl, C<sub>1-6</sub>  
                   alkylaminocarbonyl or di(C<sub>1-6</sub>)alkylaminocarbonyl.

7.     A compound selected from:

- 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[4-  
 15           (acetylamino)phenyl]methylpiperazine;  
 1-[4-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)butyl]-4-[4-  
           (acetylamino)phenyl]methylpiperazine;  
 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-(2-  
           methoxyphenyl)methylpiperazine;  
 20           1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-benzylpiperazine;  
           1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-(pyridin-3-  
           yl)methylpiperazine;  
           1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-(pyridin-2-  
           yl)methylpiperazine;  
 25           1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-(pyridin-4-  
           yl)methylpiperazine;

- 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-(4-aminophenyl)methylpiperazine;  
1-[4-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)butyl]-4-benzylpiperazine;  
1-[4-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)butyl]-4-(pyridin-2-yl)methylpiperazine;  
5 1-[4-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)butyl]-4-(pyridin-3-yl)methylpiperazine;  
1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-(4-aminophenyl)ethyl]piperazine;  
10 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-(4-(acetylamino)phenyl)ethyl]piperazine;  
1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-(imidazol-2-yl)methylpiperazine;  
1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[3-(acetylamino)phenyl]methylpiperazine;  
15 and salts and prodrugs thereof.

8. A compound selected from:

- 4-benzyl-1-[3-(5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propyl]piperazine;  
20 4-benzyl-1-[3-(5-(1,2,4-triazol-4-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propyl]piperazine;  
and salts and prodrugs thereof.

9. A compound selected from:

- 4-(4-acetylaminophenyl)methyl-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperidine;  
4-benzyl-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-1,2,5,6-tetrahydropyridine;  
25 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-(2-aminopyridin-5-yl)methylpiperazine;  
30



- 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-(4-(aminocarbonylamino)phenyl)ethyl]piperazine;  
1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-(4-cyanophenyl)methylpiperazine;
- 5 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-(4-cyanophenyl)ethyl]piperazine;  
1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-(4-(1,2,4-triazol-4-yl)phenyl)ethyl]piperazine;  
1-[3-(5-(1,2,4-triazol-1-yl)-1H-indol-3-yl)propyl]-4-[2-(4-
- 10 (acetylamino)phenyl)ethyl]piperazine;  
1-[3-(5-(1,2,4-triazol-1-yl)-1H-indol-3-yl)propyl]-4-benzylpiperazine;  
1-[3-(5-(1,2,4-triazol-1-yl)methyl)-1H-indol-3-yl)propyl]-4-benzylpiperazine;  
and salts and prodrugs thereof.
- 15 10. A compound selected from:  
1-[3-(5-(1,2,4-triazol-1-yl)methyl)-1H-indol-3-yl)propyl]-4-[2-(4-(acetylamino)phenyl)ethyl]piperazine;  
1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-(3-(acetylamino)phenyl)ethyl]piperazine;
- 20 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[4-(aminosulphonyl)phenyl]methylpiperazine;  
1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-(furan-3-yl)methylpiperazine;  
1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-(furan-2-
- 25 yl)methylpiperazine;  
1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-(thien-2-yl)methylpiperazine;  
1-benzyl-4-[(R,S)-2-hydroxy-3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;
- 30 1-[2-(4-(acetylamino)phenyl)ethyl]-4-[(R,S)-2-hydroxy-3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;

- 1-benzyl-4-[(R,S)-2-hydroxymethyl-3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;  
1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-[2-(1H-tetrazol-5-yl)phenyl]methylpiperazine;  
5 and salts and prodrugs thereof.

11. A compound selected from:

- 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-(2-phenylethyl)piperazine;  
10 4-benzyl-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;  
4-[2-(2-methyltetrazol-5-yl)phenyl]methyl-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;  
4-[2-(1-methyltetrazol-5-yl)phenyl]methyl-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;  
15 4-[2-(N-methylcarboxamido)phenyl]methyl-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;  
4-[2-(N,N-dimethylaminomethyl)phenyl]methyl-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;  
4-(but-3-enyl)-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;  
20 4-(3-methylbut-2-enyl)-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;  
4-(prop-2-enyl)-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;  
4-(prop-2-ynyl)-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;  
4-[(R,S)-1-(phenyl)carboxamidomethyl]-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;  
25 (+)-4-[1-(phenyl)carboxamidomethyl]-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;  
(-)-4-[1-(phenyl)carboxamidomethyl]-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;  
30 4-[1-(phenyl)-N-methylcarboxamidomethyl]-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;

- 4-[1-(phenyl)-N,N-dimethylcarboxamidomethyl]-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;  
4-(2-methoxycarbonylamino-1-phenylethyl)-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;  
5 4-(2-dimethylamino-1-phenylethyl)-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;  
4-[2-(4-(acetylamino)phenyl)ethyl]-1-[3-(5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propyl]piperazine;  
4-[2-(4-(acetylamino)phenyl)ethyl]-1-[3-(5-(1,2,4-triazol-4-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)propyl]piperazine;  
10 1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]-4-(4-fluorophenyl)methylpiperazine;  
4-[2-(N-methyl-N-methoxycarbonyl)amino-1-phenylethyl]-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperazine;  
15 and salts and prodrugs thereof.

12. A pharmaceutical composition comprising a compound as claimed in any one of the preceding claims in association with a pharmaceutically acceptable carrier.

20

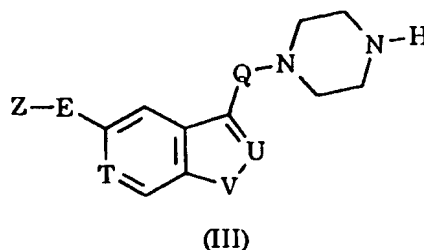
13. A compound as claimed in any one of claims 1 to 11 for use in therapy.

14. The use of a compound as claimed in any one of claims 1 to 11 for the manufacture of a medicament for the treatment and/or prevention of clinical conditions for which a subtype-selective agonist of 5-HT<sub>1D</sub> receptors is indicated.

15. A process for the preparation of a compound as claimed in any one of claims 3 to 11, which comprises:

30

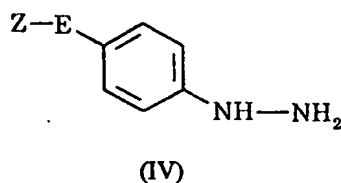
(A) attachment of the R<sup>1</sup> moiety to a compound of formula III:



5

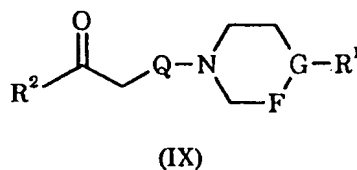
wherein Z, E, Q, T, U and V are as defined in claim 3; or

(B) reacting a compound of formula IV:



10

wherein Z and E are as defined in claim 3; with a compound of formula IX, or a carbonyl-protected form thereof:



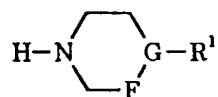
15

wherein Q, F, G, R<sup>1</sup> and R<sup>2</sup> are as defined in claim 3; followed, where required, by N-alkylation by standard methods to introduce the moiety R<sup>3</sup>; or

20

(C) reacting a compound of formula XI:

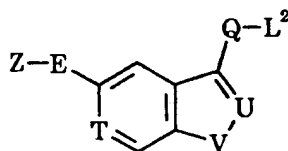
- 115 -



(XI)

wherein F, G and R<sup>1</sup> are as defined in claim 3; with a compound of formula XII:

5

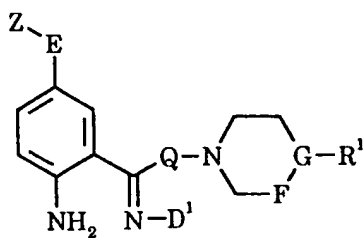


(XII)

wherein Z, E, Q, T, U and V are as defined in claim 3, and L<sup>2</sup> represents a suitable leaving group; or

10

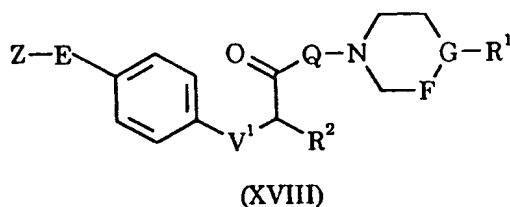
(D) cyclising a compound of formula XIV:



(XIV)

15 in which Z, E, Q, F, G, and R<sup>1</sup> are as defined in claim 3, and D<sup>1</sup> represents a readily displaceable group; or

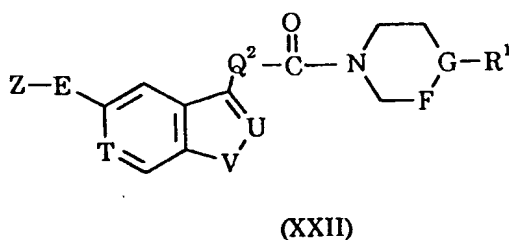
(E) cyclising a compound of formula XVIII:



wherein Z, E, Q, F, G, R<sup>1</sup> and R<sup>2</sup> are as defined in claim 3, and V<sup>1</sup> represents oxygen or sulphur; or

5

(F) reducing a compound of formula XXII:



10 wherein Z, E, T, U, V, F, G and R<sup>1</sup> are as defined in claim 3, and -Q<sup>2</sup>-CH<sub>2</sub>- corresponds to the moiety Q as defined in claim 3; and

(G) subsequently, where required, converting a compound of formula I initially obtained into a further compound of formula I by  
15 conventional methods.

16. A method for the treatment and/or prevention of clinical conditions for which a subtype-selective agonist of 5-HT<sub>1D</sub> receptors is indicated, which method comprises administering to a patient  
20 in need of such treatment an effective amount of a compound as claimed in any one of claims 1 to 11.

# INTERNATIONAL SEARCH REPORT

Inter:      Application No  
PCT/      95/01129

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6    C07D403/04    C07D401/14    C07D403/14    A61K31/40    C07D403/06  
         C07D405/14    C07D409/14    C07D471/04

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6    C07D    A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 548 813 (BRISTOL-MEYERS SQUIBB COMPANY) 30 June 1993 cited in the application see claims ---	3
A	WO,A,94 02477 (MERCK SHARP & DOHME LTD.) 3 February 1994 cited in the application see claims ---	3
A	WO,A,93 20073 (PFIZER INC.) 14 October 1993 see claims ---	3
A	EP,A,0 497 512 (MERCK SHARP & DOHME LTD.) 5 August 1992 cited in the application see claims ---	3
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \* "A" document defining the general state of the art which is not considered to be of particular relevance
- \* "E" earlier document but published on or after the international filing date
- \* "I." document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \* "O" document referring to an oral disclosure, use, exhibition or other means
- \* "P" document published prior to the international filing date but later than the priority date claimed

- \* "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \* "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \* "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \* "A" document member of the same patent family

Date of the actual completion of the international search

12 July 1995

Date of mailing of the international search report

25. 07. 95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. ( + 31-70) 340-2040, Tx. 31 651 epo nl,  
Fax ( + 31-70) 340-3016

Authorized officer

Van Bijlen, H

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 95/01129

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>EP,A,0 438 230 (MERCK SHARP &amp; DOHME LTD.)  24 July 1991  cited in the application  see claims  -----</p>	3



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/95/01129

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-548813	30-06-93	AU-B-	3003492	24-03-94
		CA-A-	2084531	20-06-93
		CZ-A-	9203592	19-01-94
		JP-A-	5262762	12-10-93
		ZA-A-	9209445	12-07-93
		CN-A-	1085556	20-04-94
-----				
WO-A-9402477	03-02-94	AU-B-	4578593	14-02-94
		CA-A-	2138649	03-02-94
		EP-A-	0651749	10-05-95
-----				
WO-A-9320073	14-10-93	AU-B-	3789893	08-11-93
		CA-A-	2133413	14-10-93
		CN-A-	1082543	23-02-94
		EP-A-	0635017	25-01-95
		JP-T-	7504919	01-06-95
		NO-A-	943762	06-10-94
-----				
EP-A-497512	05-08-92	AU-B-	644939	23-12-93
		AU-A-	1068092	06-08-92
		CN-A-	1064485	16-09-92
		JP-A-	5140151	08-06-93
		NZ-A-	241394	27-04-94
		US-A-	5298520	29-03-94
-----				
EP-A-438230	24-07-91	AU-A-	6944091	25-07-91
		CN-A-	1053429	31-07-91
		JP-A-	6100558	12-04-94
-----				

INTERNATIONAL SEARCH REPORT

national application No.

PCT/GB95/01129

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claim 16 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
Claims 1 and 2 are not defined by a chemical structure.  
Claims not searched: 1 and 2
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.